E.6 Pharmacological management

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

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

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

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

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

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

Results

Visual acuity (12 months)

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

Adverse events (12 months)

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

Notes

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

Risk of bias	Authors' judgement	Description
Adequate sequence generation?	Yes	"Random assignments were prepared by the statistical department of CIBA Vision Corp. Sealed envelopes with random assignments were prepared by the Quality Assurance Department within QLT PhotoTherapeutics Inc (Vancouver, British Columbia), which maintained independence from any other function of the trials." TAP report 1, page 1331
Allocation concealment?	Yes	"The allocation of verteporfin therapy or placebo was recorded on a randomization log that was stored in a locked cabinet with both opened and unopened randomization envelopes at each clinical center." TAP report 1, page 1331

Blinding? All outcomes	Yes	"The study coordinator aware of the treatment assignment and anyone else who might assist in the setup of verteporfin or placebo solutions were trained to make every reasonable attempt to maintain masking of the ophthalmologist, patient, vision examiner, and Photograph Reading Centre personnel. The verteporfin and placebo solutions were different colours (green vs colourless). All verteporfin and placebo solutions as well as the intravenous tubing were covered entirely with foil so that the patient and treating ophthalmologist were masked during the infusion. The ophthalmologist remained masked while administering the light since the fundus appearance during treatment does not change in any way to indicate verteporfin or placebo treatment. On the materials submitted to them, the Photograph Reading Centre graders did not have any information to indicate that verteporfin or placebo was administered. The marked hypofluorescence within a treated area noted within 1 week after verteporfin therapy in phase 1 and 2 studies is not readily apparent 3 months after treatment. Therefore, this hypofluorescence was not judged to be a likely source of potential unmasking of the graders evaluating photographs obtained at least 3 months after verteporfin therapy. Clinic monitors also had no access to information that would indicate treatment assignment. There were no known instances of unmasking of the vision examiners or Photograph Reading Centre graders. Only 2 patients who noted a green solution following extravasation of drug were likely unmasked. Treating ophthalmologists, but not the patients, were unmasked in 4 additional cases. In 2 of these cases, fluorescein angiography was obtained within 1 week after treatment to evaluate severe visual acuity decrease and showed hypofluorescence typical for verteporfin therapy. In another case the ophthalmologist noted the green verteporfin leaking onto the cover over the intravenous solution, and in 1 additional case, the ophthalmologist became unmasked prior to a vitrectomy for a subretinal hemorrhage; the patient had been assigned to placebo." TAP report 1, page 1331
Incomplete outcome data addressed? 12 month follow up	Yes	Follow-up good and equal between both groups. 94% of patients within each group completed the month 12 follow-up examination. 379/402 in verteporfin group and 194/207 in placebo group. TAP report 1, figure 1, page 1335
Incomplete outcome data addressed? 24 month follow up	Yes	Follow-up equal between both groups. 351/402 (87%) of patients PDT group completed the month 24 follow-up examination compared to 178/207 (86%) of placebo group. TAP report 2, figure 1, page 201

Free of selective reporting?	Unclear	Unlikely for primary analysis of treatment versus control but possible for subgoup analyses by lesion type. No mention of proposed subgroup analyses in power statement and discussion suggests exploratory analysis of data eg. "To explore these subgroup findings further, visual acuity distributions (Figure 9), mean change in contrast sensitivity (Table 6), and angiographic outcomes (Table 6) at the month 12 examination were evaluated, based on lesion components noted at baseline. The lesion components at baseline affected the magnitude of the treatment benefit with respect to the visual acuity distributions." TAP report 1, page 1340. The protocol for this study was not independently published prior to this first report of results but contact with the communicating author provided an assertion that subgoup analyses were planned a priori.

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

Results

Visual acuity (12 months)

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

Visual acuity (24 months)

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

Adverse events (12 months)

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

Notes

Risk of bias	Authors' judgement	Description

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

Incomplete outcome data addressed? 24 month follow up	Unclear	Follow-up a little lower in the treatment groups. 37/40 (93%) of placebo group seen at 24 months compared to 34/38 (89%) of reduced fluence group and 32/39 (82%) of the standard fluence group. Main report published Archives of Ophthalmology 2005, figure 1, page 451
Free of selective reporting?	Unclear	Primary outcome specified but secondary outcomes less clearly specified. Main outcome of interest to this review reported

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

Results

Visual acuity (12 months)

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

Visual acuity (24 months)

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

Adverse event

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

Notes

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

Risk of bias	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Patients were randomly assigned to verteporfin or placebo in a 2 : 1 ratio". Patients and methods page 1854. .
Allocation concealment?	Unclear	Not reported

Blinding? All outcomes	Unclear	"All study participants and outcome assessors were masked to the treatment assignment" Patients and methods page 1854.
Incomplete outcome data addressed? 12 month follow up	Yes	At 12 months 219/244 (90%) verteporfin and 111/364 (93%) placebo group given visual acuity assessment. Figure 1, page 1856. Missing data were imputed using last observation carried forward.
Incomplete outcome data addressed? 24 month follow up	Yes	"At month 24, 198/244 patients (81%) in the verteporfin group and 108/120 (90%) patients in the placebo group had a VA assessment (Figure 1)." Results page 1855 Missing data were imputed using last observation carried forward. Increased death rate in intervention arm attributed to chance alone.
Free of selective reporting?	Unclear	No prior publication of trial protocol

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

Results

Visual acuity (12 months)

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

Visual acuity (24 months)

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

Adverse events

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

Notes

Randomised 2:1 to verteporfin treatment.

Risk of bias	Authors' judgement	Description
Adequate sequence generation?	Yes	"Random assignments were prepared by Statprobe (Ann Arbor, MI). Statprobe also prepared sealed envelopes with random assignments and distributed them to the clinical centers. Patients were randomized in a ratio of 2:1 to verteporfin treatment or placebo (to gather more safety data on patients receiving verteporfin), with only one eye of a patient to be randomized. For cases in which

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

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

Bevacizumab vs control

Bibliographic reference	**ABC 2010** Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, et al. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ 2010;340:c2459.
Methods	**Number randomized** (total and per group): 131 participants randomly assigned to study treatment; 65 to intravitreal bevacizumab and 66 to 'standard treatment'. Standard treatment included intravitreal pegaptanib injections (n = 38), PDT with verteporfin (n = 16), or sham injection (n = 12) **Exclusions after randomization**: none

	Number analysed (total and per group): 131 total participants; 65 bevacizumab and 66 standard treatment **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: bevacizumab group: 1 participant died; standard treatment group: 3 participants withdrew from the trial and chose to have alternative treatment and 1 participant withdrew due to pain of treatment **Compliance**: limited information given: "more than 90% of patients in each group (overall 96%) were receiving treatment at the last treatment visit (48 weeks) and were followed up to week 54" **Intention to treat analysis**: yes, using last observation carried forward for 1 participant in bevacizumab group and 4 in standard treatment group **Reported power calculation**: yes; sample of 130 participants to provide power of 82% to detect or rule out a difference of 25% to 67% in outcome rates at $P < 0.05$ **Study design comment**: 'standard treatment' was not uniform; it was decided for each participant before randomization based on eligibility for NHS coverage of treatments at the time
Participants	**Country**: UK (London, England) **Age**: mean in bevacizumab group was 79 years and in standard treatment group was 81 years **Gender** (percent): 80/131 (61%) women and 51/131 (39%) men **Inclusion criteria**: age 50 years or older; primary subfoveal CNV lesion in study eye secondary to AMD; occult CNV lesions required evidence of "disease progression", based on deteriorating VA, sub- or intraretinal blood, or increase in lesion size; evidence of central macular thickening assessed using OCT; lesion in study eye with total size < 12 optic disc areas for minimally classic or occult lesions; area of fibrosis < 25% of the total lesion area; area of subretinal blood less than 50% of total lesion area; no more than 5400 microns in greater linear dimension for predominantly classic lesions; BCVA of 20/40 to 20/320 on ETDRS chart; no permanent structural damage to central fovea **Exclusion criteria**: surgery or other treatment in study eye; participation in any other clinical trial of antiangiogenic agents or (within previous month) of investigational drugs; primarily hemorrhagic lesion; coexisting ocular disease; premenopausal women not using adequate contraception; current treatment for active systemic infection; history of cardiac events (myocardial infarction, unstable angina) or cerebrovascular event in preceding 6 months; history of allergy to fluorescein; inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analysed and graded; inability to comply with study or follow up procedures **Equivalence of baseline characteristics**: yes **Diagnoses in participants**: 3/4 (75% of bevacizumab group and 76% of standard treatment group) had "minimally classic-occult" CNV; remainder of participants had predominantly classic CNV

Interventions

Intervention 1: Bevacizumab: three initial injections every 6 weeks (1.25 mg in 0.05 mL per injection).
"After the first three injections, investigators masked to treatment allocation used standardized criteria to decide whether to give further injections... Patients could therefore receive between three and nine injections over a total of 54 weeks."
PRN after first 3 injections.

1. ...patients randomized to bevacizumab received sham treatments [sham injections] if they did not require intravitreal treatment at that visit (weeks 18 to 48), according to standardized criteria for retreatment."
2. Participants who were randomized to bevacizumab in whom the usual treatment would have been photodynamic therapy...received placebo photodynamic therapy.

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

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

	Intervention 1	**Intervention 2 (standard care)**		
Agent	Bevacizumab	Pegatanib	Verteporfin PDT	Sham PDT
Dose	1.25mg	0.3mg		
Frequency	Every 6 weeks for 3 injections	Every 6 weeks for 1 year	One treatment at baseline, with further treatment based on study criteria	Sham injection every 6 weeks for a year
	PRN after first 3 injections. ...patients randomized to bevacizumab received sham treatments			

	[sham injections] if they did not require intravitreal treatment at that visit (weeks 18 to 48), according to standardized criteria for retreatment." Participants who were randomized to bevacizumab in whom the usual treatment would have been photodynamic therapy...received placebo photodynamic therapy.			

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

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

Intervals at which outcomes assessed: 1 week (safety visit), 6, 12, 18, 24, 30, 36, 42, 48 weeks (treatment or assessment for treatment), 1 year (54 weeks)

Results

Visual acuity

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

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

Adverse event

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

Notes

Full study name: The Avastin® (Bevacizumab) for Choroidal Neovascularization (ABC) Trial
Type of study: published
Funding sources: special trustees of Moorfields Eye Hospital; Department of Health through an award by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology; additional support from the National Eye Research Centre, Bristol
Declarations of interest: "The authors who work at Moorfields Eye Hospital have no financial gain from this endeavour, and no patents or patent applications with regard to bevacizumab are owned by the authors or Moorfields Pharmaceuticals."; "The pharmaceutical division at Moorfields (Moorfields Pharmaceuticals) is involved in the repackaging of bevacizumab for

	intraocular use for sale to other institutions."; various authors reported being on advisory boards for Novartis, Pfizer, GSK, MSD, and/or Allergan; receiving research grants for investigator sponsored trials, money, travel grants, and/or lecture fees from Novartis; and/or being a shareholder of a software company that has business links with Novartis and Pfizer **Study period**: August 2006 to November 2008 (enrolment Aug 2006 to November 2007) **Reported subgroup analyses**: by type of neovascular lesion (minimally classic/occult; predominantly classic); type of standard treatment **Contacting study investigators**: trial authors contacted; no additional information provided for this review

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

Other bias	Low risk	The standard therapy group did not receive the same intervention (PDT, pegaptanib injection, or sham injection).

Bibliographic reference	**Sacu 2009** Sacu S, Michels S, Prager F, Weigert G, Dunavoelgyi R, Geitzenauer W, et al. Randomised clinical trial of intravitreal Avastin® vs photodynamic therapy and intravitreal triamcinolone: long-term results. Eye 2009;23(12):2223-7.
Methods	**Number randomized (total and per group):** 28 participants randomly assigned to study treatment; 14 in bevacizumab group and 14 in PDT + IVTA group **Exclusions after randomization**: none **Number analysed (total and per group**): 28 total participants; 14 in bevacizumab group and 14 in PDT + IVTA group **Unit of analysis:** individuals (one study eye per participant) **Losses to follow up**: one participant in PDT + IVTA group did not complete 6 or 12 month visits **Compliance**: not reported; no participant was excluded up to 12 months **Intention to treat analysis**: yes, although the paper does not state how data were imputed for the participant missing the 6 and 12 month follow-up visits in the PDT + IVTA group **Reported power calculation**: yes, sample of 14 participants per group for power of 80% Study design comment: bevacizumab group had more follow-up visits than the PDT + IVTA group
Participants	**Country**: Vienna, Austria **Age**: mean 78 years (range 58 to 88) **Gender (percent):** 19/28 women (68%) and 9/28 men (32%) **Inclusion criteria**: participants with neovascular AMD of any lesion type; lesion smaller than four disc areas; no prior treatment for neovascular AMD; VA of 20/40 to 20/800 **Exclusion criteria**: participants with a history of thromboembolic events within the past 3 months and predictable need for ocular surgery **Equivalence of baseline characteristics**: yes **Diagnoses in participants**: neovascular AMD

<table>
<tr><td>Interventions</td><td>
Intervention 1: 1 mg intravitreal bevacizumab injections; after 3 initial injections at monthly intervals re-treatment was based on OCT findings only (evidence of persistent or recurrent intra- or subretinal fluid); participants seen at monthly intervals
Intervention 2: standard verteporfin PDT plus same day 4 mg intravitreal triamcinolone acetonide; re-treatment at 3 months if there was evidence of leakage by fluorescein angiography
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Verteporfin PDT plus intravitreal triamcinolone acetonide (same day)</td></tr>
<tr><td>Dose</td><td>1 mg</td><td>Standard PDT, 4 mg triamcinolone</td></tr>
<tr><td>Frequency (interval)</td><td>Monthly</td><td></td></tr>
<tr><td></td><td>After 3 initial injections at monthly intervals re-treatment was based on OCT findings only</td><td>Re-treatment at 3 months if there was evidence of leakage by fluorescein angiography</td></tr>
</table>
Length of follow up: Planned: 12 months; Actual: 12 months
</td></tr>
<tr><td>Outcomes</td><td>
Primary outcome, as defined: change in mean visual acuity
Secondary outcomes, as reported: change in mean 1 mm central retinal thickness; BCVA; StratusOCT; fluorescein angiography; indocyanine green angiography; microperimetry
Adverse events
Intervals at which outcomes assessed: baseline, months 1, 3, 6, and 12
</td></tr>
<tr><td>Results</td><td>
Visual acuity
<table>
<tr><th></th><th>Bevacizumab (n=14)</th><th>PDT + IVTA (n=14)</th><th>RR (95% CI)</th></tr>
<tr><td>Gain ≥15 letters , n(%)</td><td>4 (29)</td><td>1 (7)</td><td>4.00 (0.51, 31.46)</td></tr>
<tr><td>Gain <15 letters (0-14), n(%)</td><td>7</td><td>4</td><td>1.75 (0.66, 4.66)</td></tr>
<tr><td>Loss <15 letters, n(%)</td><td>3</td><td>7</td><td>0.43 (0.14, 1.33)</td></tr>
<tr><td>Loss ≥ 15 letters</td><td>0</td><td>2</td><td>0.20 (0.01, 3.82)</td></tr>
</table>
</td></tr>
</table>

	Mean VA in bevacizumab treated eyes improved from 50 letters at baseline to 58 letters at month 12; changes of mean VA in the PDT+IVTA-treated eyes were 46 letters at baseline to 43 letters at month 12.
Notes	**Type of study**: published **Funding sources**: not reported **Declarations of interest**: one investigator reported being "an owner of the patent on the use of green porphyrins in neovasculature of the eye under the guidelines of the Wellman Laboratories of Photomedicine, Harvard Medical School, Boston, MA, USA" **Study period**: not reported **Reported subgroup analyses**: none **Contacting study investigators**: trial authors contacted and contributed information for this review

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

Masking of outcome assessment (detection bias)	High risk	"Patients in the PDT + IVTA groups had characteristic post-treatment hypofluorescence within the area of the PDT treatment spot..."
Incomplete outcome data (attrition bias)	High risk	Intent-to-treat analysis was followed.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Low risk	None observed

Rnibizumba vs control

Ranibizumab vs PDT

Bibliographic reference	**ANCHOR 2006** Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim R, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. New England Journal of Medicine 2006;355(14):1432-44.
Methods	**Number randomized (total and per group):** 423 participants randomly assigned to study treatment; 140 to 0.3 mg ranibizumab, 140 to 0.5 mg ranibizumab, and 143 to verteporfin PDT **Exclusions after randomization**: 3 participants in the 0.3 mg ranibizumab group did not receive treatment after randomization, one because of participant's decision and two based on physician's decision **Number analyzed (total and per group):** 422 total participants; 140 in 0.3 mg ranibizumab group, 139 in 0.5 mg ranibizumab group, and 143 in verteporfin PDT group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 10 in 0.3 mg ranibizumab group, 5 in 0.5 mg ranibizumab group, and 10 in verteporfin PDT group; reasons included death, adverse events, loss to follow up, participant's decision, physician's decision and participant non-compliance **Compliance**: limited information given: "more than 90% of patients in each group (91.5% overall) were receiving treatment at 12 months" **Intention to treat analysis**: yes, using last observation carried forward for missing data

	Reported power calculation: yes, sample of 426 participants to provide power of 96% to detect or rule out differences in proportion of participants losing less than 15 letters at 12 months assuming 67% of participants in the PDT control arm and 84% in the ranibizumab arms will have that outcome (? ? 0.05). **Study design comment**: randomization stratified by study center and baseline visual acuity
Participants	**Country:** USA, France, Germany, Hungary, Czech Republic, and Australia (83 study centers) **Age**: mean (range) was 77 years (54 to 97) in 0.3 ranibizumab group, 76 years (54 to 93) in 0.5 mg ranibizumab group, and 78 years (53 to 95) in verteporfin PDT group **Gender (percent):** 211/423 (50%) women and 212/423 (50%) men **Inclusion criteria**: age 50 years or older; subfoveal CNV lesion secondary to AMD determined independently based on fluorescein angiography and fundus photography to be predominantly classic in composition and suitable for treatment with verteporfin PDT; ≥ 5400 microns in greater linear dimension; BCVA of 20/40 to 20/320 Snellen using equivalent ETDRS charts; no permanent structural damage to central fovea; participants with juxta- or extrafoveal photocoagulation in the study eye more than 1 month prior to day 0 and prior verteporfin PDT in the non-study eye more than 7 days before study day 0 were included **Exclusion criteria**: surgery or other treatment in study eye; treatment with verteporfin PDT in the non-study eye less than 7 days preceding study day 0; participation in any other clinical trial of antiangiogenic agents or (within previous month) of investigational drugs; subretinal hemorrhage in study eye 50% or more of lesion area; subfoveal fibrosis or atrophy in study eye; coexisting ocular disease; premenopausal women not using adequate contraception; current treatment for active systemic infection; history of other disease, metabolic dysfunction, or physical examination or laboratory finding giving reasonable suspicion of a condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or place the participant at a high risk for complications; history of allergy to fluorescein; inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed and graded; inability to comply with study or follow-up procedures **Equivalence of baseline characteristics**: a slightly higher percentage of participants in 0.3 mg ranibizumab group were aged 75-84 years (60% compared with 45.7% in 0.5 mg group and 51.7% in verteporfin PDT group) **Diagnoses in participants**: 410/423 (97%) had predominantly classic CNV (> 95% of each treatment group); 12/423 (3%) had minimally classic CNV; and 1/423 (0.2%) had occult with no classic CNV
Interventions	**Intervention 1**: 0.3 mg ranibizumab monthly intravitreal injections plus sham verteporfin PDT (intravenous infusion of saline followed by laser irradiation of macula), need for retreatment based on assessment of fluorescein angiograms at 3-month intervals

Intervention 2: 0.5 mg ranibizumab monthly intravitreal injections plus sham verteporfin PDT when needed for retreatment, as above
Intervention 3: sham intravitreal injection plus active verteporfin PDT (laser irradiation of macula following intravenous administration of verteporfin)
Ranibizumab was injected into the study eye at monthly intervals (ranging from 23 to 37 days) for a total of 12 injections in the first year beginning on day 0. Either verteporfin or sham verteporfin PDT was administered on day 0 and then if needed on the basis of investigators' evaluation of angiography at months 3, 6, 9, or 12.

	Intervention 1	**Intervention 2**	**Intervention 3**
Agent	Ranibizumab +sham PDT	Ranibizumab + sham PDT	PDT + sham injection
Dose	0.3mg	0.5mg	
Frequency	Monthly	Monthly	
			administered on day 0 and then if needed on the basis of investigators' evaluation of angiography at months 3, 6, 9, or 12

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

Outcomes

Primary outcome, as defined: proportion of participants losing fewer than 15 letters from baseline visual acuity in the study eye at 12 months
Secondary outcomes reported: proportion of participants gaining 15 letters or more from baseline; proportion of participants with a Snellen equivalent of 20/40 or better; proportion of participants with a Snellen equivalent of 20/200 or worse; mean change from baseline (letters over time); mean change from baseline to month 12 in the size of the classic CNV component and total area of leakage from CNV

Exploratory efficacy endpoints: loss of 30 letters or more of visual acuity, mean changes in area of CNV and area of the entire lesion
Safety assessments: IOP measurement before and 50 to 70 minutes after each study treatment, ocular and non-ocular adverse events, changes and abnormalities in clinical laboratory parameters and vital signs, and immunoreactivity to ranibizumab
Quality-of-life indicators
Intervals at which outcomes were assessed: "at regularly scheduled study visits," 12 and 24 months, angiography evaluation was performed at months 3, 6, 9, 12

Results

Visual acuity (at 12 month follow-up)

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

Visual acuity (24 months)

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

Adverse event (24 months)

	0.3mg ranibizumab (n=140)	0.5mg ranibizumab (n=140)	PDT (n=143)
Presumed endophthalmitis, no.	0	3	0
Rhegmatogenous retinal detachment	1	2	0

Vitreous haemorrhage	0	2	0
Ocular inflammation	8	14	1
Cataract	23	27	15
Treatment-emergent hypertension	13	17	23
Arterial thromboembolic event (nonfatal)	4	5	4
Death (vascular & nonvascular)	5	3	5
Non-ocular haemorrhage	16	16	8

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

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	A dynamic randomization method was used, stratified by study centre and visual acuity scores on day 0 (< 45 letters vs >= 45 letters). "Dynamic randomization, a generalization of the hierarchical method proposed by Signorini, et al. (1993)" (email communication with Genentech, dated 24 October 2007)
Allocation concealment (selection bias)	Low risk	"A centralized IVRS was used to conduct the randomization. Participants, study site personnel, and Sponsors' personnel were masked to the treatment assignment throughout the study, except for the injecting physician, designated unmasked site personnel, and Sponsors' drug accountability monitors." (email communication with Genentech, dated 24 October 2007)
Masking of participants (performance bias)	Low risk	"To maintain masking, patients who had received saline as well as those who had received verteporfin were instructed to follow exposure-to-light-precautions after PDT administration according to the verteporfin package insert." "An empty, needle-less syringe was used for sham injections, with pressure applied to the anesthetized and prepared eye at the site of a typical intravitreal injection. Pre- and post-injection procedures (described previously) were identical for ranibizumab and sham injections."
Masking of study personnel (performance bias)	Low risk	"The "injecting" ophthalmologist administering the study treatments was unmasked. All other study site personnel (except those assisting with study treatment administration), patients, and central reading centre personnel were masked to treatment assignment."
Masking of outcome assessment (detection bias)	Low risk	"Double masking of treatment assignment necessitated at least two investigators per study site: an unmasked "injecting" ophthalmologist to administer the study treatments and a masked "evaluating" ophthalmologist to perform study assessments."
Incomplete outcome data (attrition bias)	Low risk	"Efficacy analyses were performed on an intent-to-treat basis (including all randomized patients and according to the treatment group to which they were assigned) using a last-observation-carried-forward method to impute missing data (primary analysis) and using observed data (exploratory sensitivity analysis)."
Selective reporting (reporting bias)	Low risk	We did not have access to the protocol. However, primary and secondary outcomes reported to the FDA were reported in the publication with no changes.
Other bias	Unclear risk	Sponsored by Genentech and Novartis Pharma.

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

<table>
<tr><td>Bibliographic reference</td><td>LAPTOP 2013

Oishi A, Kojima H, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Fujihara M, Bessho N, Uenishi M, Kurimoto Y, and Negi A. 2013. "Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results". American Journal of Ophthalmology 156(4):644-51.</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><th></th><th>Photodynamic therapy (n=47)</th><th>Ranibizumab (n=46)</th><th>P values</th></tr>
<tr><td>Mean age, year (SD)</td><td>75.0 (8.0)</td><td>75.4 (6.9)</td><td>0.80</td></tr>
<tr><td>% of female (n)</td><td>15 (31.9)</td><td>18 (39.1)</td><td></td></tr>
<tr><td>BCVA (logMAR unit (SD)</td><td>0.57 (0.31)</td><td>0.48 (0.27)</td><td>0.12</td></tr>
<tr><td>BCVA Snellen equivalence, n(%)</td><td></td><td></td><td></td></tr>
<tr><td>≤0.1 (20/200)</td><td>7 (14.9)</td><td>5 (10.9)</td><td></td></tr>
<tr><td>>0.1 (20/200 but <0.5 (20/40)</td><td>24 (51.1)</td><td>24 (52.2)</td><td></td></tr>
<tr><td>≥0.5 (20/40)</td><td>16 (34.0)</td><td>17 (37.0)</td><td></td></tr>
</table></td></tr>
<tr><td>Methods</td><td>Study visits and procedures:
Patients were randomised in a1:1 ratio to either vertiporfin PDT (6mg/m^2) or ranibizumab monotherapy (0.5mg). As the initial treatment, patients in PDT group underwent verteporfin injection and laser irradiation. Patients in the ranibizumab group underwent 3 monthly ranibizumab injection.
After the initial treatment, repeat treatment was applied as need (pro re nata)</td></tr>
<tr><td></td><td>Intervention 1: vertiporfin PDT</td></tr>
<tr><td></td><td>Intervention 2: ranibizumab</td></tr>
<tr><td></td><td>Outcomes: primary outcome: the proportion of patients in each group gaining or losing logMAR of more than 0.2 at 24 months; secondary outcome: central retinal thickness and the outer border of the retinal pigment epithelium measure with OCT.</td></tr>
<tr><td></td><td>Analyses: Chi-square test was used to compare the percentage of patients with gained, unchanged or lost VA. Two-way repeated-measures analysis of variance was used to investigate the difference in mean VA or CRT.</td></tr>
<tr><td></td><td>Length of follow up: 12 months</td></tr>
</table>

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

Results

	Photodynamic therapy (n=47)	**Ranibizumab (n=46)**	**Effect (relative risk, 95%CI)**
Change in logMAR, n(%)			
No change	15 (31.9)	20 (43.5)	
Decrease			
≥0.1 but <0.2 unit (equivalent to more than 1 line but fewer than 2 lines=more than 5 letters fewer than 10 letter)	4 (8.5)	1 (2.2)	
≥0.2 but <0.3 unit	0 (0)	1 (2.2)	
Fewer than 15 letters	4 (8.5)	2 (4.3)	1.96 (0.38 to 10.17)
≥0.3 but <0.4 unit	8 (17.0)	3 (6.5)	
≥0.4 but <0.5 unit	1 (2.1)	0 (0)	
≥0.5 but <0.6 unit	2 (4.3)	0 (0)	
≥0.6 unit	2 (4.3)	0 (0)	
15 letters or more loss	15 (31.9)	4 (8.6)	3.67 (1.32 to 10.23)
30 letters or more loss	2 (4.3)	0 (0)	
Increase			
≥0.6 unit (30 letters or more)	2 (4.3)	1 (2.2)	1.96 (0.18 to 20.85)
≥0.5 but <0.6 unit	1 (2.1)	0(0)	
≥0.4 but <0.5 unit	0(0)	2(4.3)	

Bibliographic reference	**LAPTOP 2013** Oishi A, Kojima H, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Fujihara M, Bessho N, Uenishi M, Kurimoto Y, and Negi A. 2013. "Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results". American Journal of Ophthalmology 156(4):644-51.
	≥0.3 but <0.4 unit: 2 (4.3); 5 (10.9) 15 letters or more gain: 5 (10.6); 8 (17.4); 0.61 (0.22, 1.73) ≥0.2 but <0.3 unit: 3 (6.4); 5(10.9) ≥0.1 but <0.2 unit: 7(14.9); 8(17.4) Less than 15 letters gain: 10 (21.3); 13 (28.3); 0.75 (0.37 to 1.54)
	Missing data handling/loss to follow up: 4 patients did not complete the initial 3-month treatment
Comments	**Was allocation adequately concealed?**
	Was knowledge of the allocated intervention adequately prevented during the study? unclear
	Was the allocation sequence adequately generated? unclear
	Was the study apparently free of other problems that could put it at a high risk of bias? None observed
	Were incomplete outcome data adequately addressed? "We excluded patients who did not complete the initial 3-month follow-up from final analysis. For the rest of the patients, we applied intention-to-treat analysis policy.
	Are reports of the study free of suggestion of selective outcome reporting? Results were reported for primary and secondary outcomes specified in the Methods section

Ranibizumab vs sham

Bibliographic reference	**MARINA 2006**

	Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006;355(14):1419-31.
Methods	**Number randomized (total and per group):** 716 participants randomly assigned to study treatment; 238 to 0.3 mg ranibizumab group, 240 to 0.5 mg ranibizumab group, and 238 to sham injection group **Exclusions after randomization**: none **Number analysed (total and per group):** all 716 participants; 238 to 0.3 mg ranibizumab group, 240 to 0.5 mg ranibizumab group, and 238 to sham injection group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 52 participants did not complete 12 months: 12 in the 0.3 mg ranibizumab group, 14 in the 0.5 mg ranibizumab group, and 26 in the sham injection group. Reasons included death, adverse events, loss to follow up, participant's decision, physician's decision, participant non-compliance, and need for other therapeutic intervention. **Compliance**: "more than 90% of patients in each treatment group remained in the study at 12 months, and approximately 80 to 90% remained at 24 months" **Intention to treat analysis:** yes, using last observation carried forward for missing data **Reported power calculation**: yes, sample of 720 participants for power of 95% **Study design comment**: following primary analyses of the study at one year and with recommendation of the data monitoring committee, the study protocol was amended to offer treatment with 0.5 mg ranibizumab to participants still being followed in the sham control group. The study protocol was amended four months into the study to allow photodynamic therapy for active minimally classic or occult with no classic lesions that were no larger than 4 disc areas in size and accompanied by a 20-letter or greater loss from baseline visual acuity confirmed at consecutive study visits. When photodynamic therapy was used, the scheduled study treatment was postponed until the next scheduled monthly study visit
Participants	**Country:** USA **Age**: range 52 to 95 years; mean was 77 years in each of the three treatment groups **Gender (percent**): 464/716 (65%) women and 252/716 (35%) men **Inclusion criteria:** age 50 years or older; active primary or recurrent subfoveal lesions with CNV secondary to AMD defined as: (1) exhibiting at least a 10% increase in lesion size determined by comparing a fluorescein angiogram performed within 1 month preceding study day 0 with a fluorescein angiogram performed within 6 months preceding study day 0, (2) resulting in a visual acuity loss of greater than 1 Snellen line any time within the prior 6 months, or (3) subretinal hemorrhage associated with CNV within 1 month preceding study day 0; total area of CNV encompassed

<table>
<tr><td></td><td>within the lesion at least 50% of the total lesion area; total lesion area of 12 disc areas or less in size; best-corrected visual acuity of 20/40 to 20/320 (Snellen equivalent on ETDRS chart). Participants with lesions with an occult CNV component were included, but for participants with concomitant classic CNV, the area of classic CNV must have been less than 50% of the total lesion size.
Exclusion criteria: prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy in the study eye; previous participation in a clinical trial involving antiangiogenic drugs; treatment with verteporfin in the non-study eye less than 7 days preceding study day 0; previous intravitreal drug delivery or subfoveal focal laser photocoagulation in the study eye; laser photocoagulation in the study eye within 1 month preceding study day 0; history of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in study eye; participation in any studies of investigational drugs within 1 month preceding study day 0; subretinal hemorrhage in study eye involving center of the fovea if the size of hemorrhage is either 50 % or more of the total lesion area or 1 or more disc areas in size; subfoveal fibrosis or atrophy in study eye; CNV in either eye due to other causes; retinal pigment epithelia tear involving the macula in the study eye
Equivalence of baseline characteristics: yes
Diagnoses in participants: 1/716 (0.1%) had predominantly classic CNV; 264/716 (37%) had minimally classic CNV; and 451/716 (63%) had occult with no classic CNV</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 0.3 mg ranibizumab intravitreal injection monthly for 2 years
Intervention 2: 0.5 mg ranibizumab intravitreal injection monthly for 2 years
Intervention 3: sham injection monthly for 2 years
In all intervention groups, verteporfin photodynamic therapy for the study eye was allowed if the choroidal neovascularization converted to a predominantly classic pattern.
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention3</th></tr>
<tr><td>Agent</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Sham injection</td></tr>
<tr><td>Dose</td><td>0.3 mg</td><td>0.5mg</td><td>-</td></tr>
<tr><td>Frequency</td><td>Monthly for2 years</td><td>Monthly for 2 years</td><td>Monthly for 2 years</td></tr>
<tr><td></td><td colspan="3">verteporfin photodynamic therapy for the study eye was allowed if the choroidal neovascularization converted to a predominantly classic pattern</td></tr>
</table>
Length of follow up: Planned: 2 years; Actual: 2 years</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)</td></tr>
</table>

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

Visual acuity (24 months)

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

Adverse events (24 months)

	0.3mg ranibizumab (n=238)	0.5mg ranibizumab (n=240)	Sham injection (n=238)
Presumed endophthalmitis, no.	2	3	0
Rhegmatogenous retinal detachment	0	0	1
Vitreous haemorrhage	1	1	2
Ocular inflammation	40	50	30
Cataract	37	37	37
Treatment-emergent hypertension	41	39	38
Arterial thromboembolic event (nonfatal)	9	9	6
Death (vascular & nonvascular)	5	6	6

	Non-ocular haemorrhage	25	26	15
Outcomes	**Primary outcomes**, as defined: proportion of participants who lost fewer than 15 letters from baseline visual acuity in study eye at 12 months **Secondary outcomes**, as defined: proportion of participants who gained 15 letters or more from baseline, proportion of participants with a Snellen equivalent of 20/200 or worse, and mean change from baseline (letters over time); mean change from baseline to month 12 in the size of the classic CNV component and total area of leakage from CNV **Exploratory efficacy end points**: proportion of participants with visual acuity 20/40 or better, and 20/20 at 12 and 24 months (Snellen equivalent), total area of and change from baseline CNV lesion, area of leakageAdverse events, including ocular and non-ocular adverse events and proportion of participants developing immunoreactivity to ranibizumab, intraocular inflammation, and IOP **Safety assessments**: IOP measurement 60 minutes after each injection, incidence and severity of ocular and non-ocular adverse events, changes and abnormalities in clinical laboratory parameters and vital signs, and immunoreactivity to ranibizumab **Intervals at which outcomes assessed**: 12 and 24 months			
Notes	**Full study name**: Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration **Type of study**: published **Funding sources**: Genentech, USA and Novartis Pharma, Switzerland **Declarations of interest**: various authors reported having received consulting fees from Genentech, Eyetech, Novartis Ophthalmics, Novartis, QLT, Alcon Laboratories, Pfizer, Regeneron, Theragenics, VisionCare, Protein Design Labs, Allergan, BioAxone, Tanox, Genaera, Jerini, Oxigene, Quark, Genzyme, iScience, ISTA, and Athenagen; lecture fees from Genentech, Eyetech, Pfizer, Jerini, Allergan, and Novartis Ophthalmics; grant support from Genentech, Novartis, Eyetech, Pfizer, Theragenics, and Genaera and Alcon Laboratories; and/or equity interest in Pfizer and/ or being employees of Genentech and owning Genentech stock **Study period**: enrolment March 2003 to December 2003 Reported subgroup analyses: by baseline lesion (4 or fewer optic-disk areas; more than 4), type of lesion (minimally classic; occult with no classic), and baseline VA (less than 55 letters; 55 or more letters) **Contacting study investigators**: trial authors contacted and contributed information for this review			

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomly assigned in a 1:1:1 ratio, using a dynamic randomization algorithm, to receive ranibizumab (LUCENTIS®, Genentech, Inc., South San Francisco, CA) 0.3 or 0.5 mg or a sham injection monthly (30±7 days) for 2 years (24 injections). Randomization was stratified by baseline visual acuity score (<55 letters [approximately worse than 20/80] vs. ≥ 55 letters) at day 0, by choroidal neovascularization subtype (minimally classic or occult with no classic), and by study centre."
Allocation concealment (selection bias)	Low risk	"A centralized interactive voice response system (IVRS) was used to handle the randomization" (email communication with Genentech, dated 24 October 2007).
Masking of participants (performance bias)	Low risk	"All other study site personnel (except those assisting with injections), patients, and central reading centre personnel were masked to treatment assignment."
Masking of study personnel (performance bias)	Low risk	"Masking of treatment assignment required at least two investigators per study site: an evaluating physician (masked to treatment assignment), and an injecting physician (unmasked regarding ranibizumab or sham treatment but masked to ranibizumab dose)."
Masking of outcome assessment (detection bias)	Low risk	"All other study site personnel (except those assisting with injections), patients, and central reading centre personnel were masked to treatment assignment."
Incomplete outcome data (attrition bias)	Low risk	"Efficacy analyses were performed on an intent-to-treat basis (all randomized patients) using a last observation carried forward method to handle missing data."
Selective reporting (reporting bias)	Low risk	We did not have access to the protocol. We matched all outcomes reported in publications with those reported to the FDA.
Other bias	Unclear risk	Sponsored by Genentech and Novartis Pharma. The study authors disclosed financial interests and/or were paid consultants, employees, and/or shareholders of the funding companies.

Bibliographic reference	Pier 2008 Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. American Journal of Ophthalmology 2008;145(2):239-48.

Methods	**Number randomized (total and per group**): 184 participants randomly assigned to study treatment; 60 to 0.3 mg ranibizumab, 61 to 0.5 mg ranibizumab, and 63 to sham injection **Exclusions after randomization**: one participant in the 0.3 mg ranibizumab group withdrew from the study prior to receiving first treatment and was excluded **Number analyzed (total and per group):** 183 participants; 59 in the 0.3 mg ranibizumab, 61 in the 0.5 mg ranibizumab, and 63 in the sham injection group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 13 participants did not complete 12 months: 1 in the 0.3 mg ranibizumab group, 2 in the 0.5 mg ranibizumab group, and 8 in the sham injection group. Reasons included participant's decision, participant non-compliance, and need for other therapeutic intervention. **Compliance:** "...treatment compliance was good in the ranibizumab groups, with 85% or more of subjects receiving each scheduled injection. In the sham group, 27% of subjects permanently discontinued treatment before month 12, most often because the subject's condition mandated another therapeutic intervention." **Intention to treat analysis (Y/N**): yes, using last observation carried forward for missing data **Reported power calculation**: yes, sample of 180 participants for power of 90% **Study design comment:** following reports of other clinical trials, the study protocol was amended (February 2006) to offer treatment with 0.5 mg ranibizumab to participants in the sham control group who had completed 12 months of follow up and were still being followed. The study protocol was amended again (August 2006) to switch participants in the 0.3 mg ranibizumab group to receive 0.5 mg ranibizumab, to change assessments for all participants from quarterly to monthly after month 12, and to allow treatment with ranibizumab in the fellow eyes.
Participants	**Country**: USA (43 study centres) **Age**: range 54 to 94 years; mean was 79 years in each ranibizumab treatment group and 78 years in the sham injection group **Gender (percent):** 110/184 (60%) women and 74/184 (40%) men **Inclusion criteria**: age 50 years or older; primary or recurrent subfoveal CNV secondary to AMD, with total CNV area (classic plus occult CNV) 50% or more of the total lesion area and total lesion size 12 or fewer disc areas; best-corrected visual acuity of 20/40 to 20/320 (Snellen equivalent on ETDRS chart). participants with minimally classic or occult with no classic CNV were included if they had 10% or more increase in lesion size between one and six months prior to day 0, one or fewer Snellen line (or equivalent) VA loss within the prior six months, or CNV-associated subretinal hemorrhage within one month before day zero.

<table>
<tr><td></td><td>Exclusion criteria: prior treatment with verteporfin photodynamic therapy, external-beam radiation therapy, transpupillary thermotherapy, or subfoveal laser photocoagulation (or juxtafoveal or extrafoveal laser photocoagulation within one month before day zero); subretinal hemorrhage in the study eye involving the center of the fovea, if the size of the hemorrhage is either 50% or more of the total lesion area or one or more disk areas in size; previous inclusion in antiangiogenic drug trial; prior treatment with photodynamic therapy in non-study eye within seven days before day zero.
Equivalence of baseline characteristics: yes
Diagnoses in participants: 35/184 (19%) had predominantly classic CNV; 69/184 (38%) had minimally classic CNV; 79/184 (43%) had occult with no classic CNV; and 1/184 (< 1%) could not be classified</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 0.3 mg ranibizumab intravitreal injection every month for first three doses (day 0, months one and two), followed by doses every three months (months 5, 8, 11, 14, 17, 20, and 23)
Intervention 2: 0.5 mg ranibizumab intravitreal injection every month for first three doses (day 0, months one and two), followed by doses every three months (months 5, 8, 11, 14, 17, 20, and 23)
Intervention 3: sham injection every month for first three doses (day 0, months one and two), followed by doses every three months (months 5, 8, 11, 14, 17, 20, and 23)
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention 3</th></tr>
<tr><td>Agent</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Sham injection</td></tr>
<tr><td>Dose</td><td>0.3 mg</td><td>0.5 mg</td><td>-</td></tr>
<tr><td>Frequency</td><td>Monthly</td><td>Monthly</td><td>monthly</td></tr>
<tr><td></td><td colspan="3">All interventions had monthly injection for first 3 doses, followed by doses every 3 months.</td></tr>
</table>
Length of follow up: Planned: 2 years; Actual: 2 years</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)
<table>
<tr><th></th><th>0.3mg ranibizumab (n=60)</th><th>0.5mg ranibizumab (n=61)</th><th>Sham injection (n=63)</th></tr>
<tr><td>Gain of ≥15 letters, n(%)</td><td>7 (11.7)</td><td>8 (13.1)</td><td>6 (9.5)</td></tr>
<tr><td>Loss of <15 letters</td><td>50 (83.3)</td><td>55 (90.2)</td><td>31 (49.2)</td></tr>
</table></td></tr>
</table>

	Adverse event (12 months) 0.3mg ranibizumab (59) / 0.5mg ranibizumab (n=61) / Sham injection (n=63) Ocular haemorrhage: 2 / 0 / 2 Macular odema: 1 / 0 / 2 Ocular inflammation: 4 / 2 / 3 Cataract: 3 / 4 / 4 Hypertension: 4 / 6 / 5
Outcomes	**Primary outcomes**, as defined: mean change from baseline to 12 months in visual acuity score **Secondary outcomes**, as defined: proportion of participants losing 15 letters or fewer from baseline; proportion of participants gaining 15 letters or greater from baseline; proportion of participants with a Snellen equivalent of 20/200 or worse; mean change from baseline in the near activities, distance activities, and vision-specific dependency NEI VFQ-25 subscales; and mean change from baseline in total area of CNV and total area of leakage from CNV (based on central reading center assessment) **Exploratory efficacy end points**: proportion of participants who had lost 30 letters or fewer from baseline VA at 12 months; mean change in visual acuity score from baseline to three months; mean change in visual acuity score from three months to 12 months **Adverse events** **Safety assessments**: incidence and severity of ocular and non-ocular adverse events, changes in vital signs, incidence of positive serum antibodies to ranibizumab, IOP measurement 60 minutes after each injection **Intervals at which outcomes assessed**: injection visits at day 0 and months 1, 2, 3, 8, 11, 14, 17, 20, and 23; clinic visits at months 3, 12, and 24
Notes	**Full study name**: A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration **Type of study**: published **Funding sources:** Genentech, USA and Novartis Pharma, Switzerland **Declarations of interest**: various authors reported receiving consulting fees from Genentech, Novartis, OSI/Eyetech, Eyetech/Pfizer, Novartis, and Alcon; lecture fees from Genentech, Novartis, OSI/Eyetech, Eyetech/Pfizer; and grant

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

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

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

Bevacizumab vs ranibizumab

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

<table>
<tr><td></td><td>Age: not reported for 120 enrolled participants (mean 64.4 years in analyzed bevacizumab group; mean 63.5 years in analyzed ranibizumab group)
Gender (percent): not reported for 120 enrolled participants (28/50 (56%) men and 22/50 (44%) women in analyzed bevacizumab group; 22/54 (41%) men and 32/54 (59%) women for analyzed ranibizumab group)
Inclusion criteria: age 50 years or older; presence of subfoveal or juxtafoveal CNV of any type; active leakage pattern; baseline BCVA between 35 and 70 ETDRS letters; baseline central macular thickness greater than or equal to 250 ?m, as measured by OCT
Exclusion criteria: previous treatment for CNV in either eye; macular scarring; any coexisting other ocular disease or pathology; monocular patients; history of ocular surgery within six months of enrolment; history of cerebrovascular accident and myocardial infarction
Equivalence of baseline characteristics: gender imbalance between analysed groups
Diagnoses in participants: all with subfoveal or juxtafoveal CNV; 22/50 participants with occult CNV in bevacizumab group and 24/54 participants with occult CNV in ranibizumab group</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg intravitreal bevacizumab every month for first three months; re-treatment afterwards based on OCT or VA changes
Intervention 2: 0.5 mg intravitreal ranibizumab every month for first three months; re-treatment afterwards based on OCT or VA changes
<table>
<tr><th></th><th>Intervention1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>monthly</td><td>monthly</td></tr>
<tr><td></td><td colspan="2">Treatment for first 3 months, and re-treatment afterwards based on OCT or VA changes</td></tr>
</table>
Length of follow up: Planned: 18 months; Actual: 18 months</td></tr>
<tr><td>Outcomes</td><td>Primary outcomes, as defined: "changes in BCVA and CMT from baseline (month 0) to month 18"
Secondary outcomes, as reported: blood pressure measurements; reports of unusual extremity pain
Adverse events
Intervals at which outcome assessed: monthly through 18 months</td></tr>
</table>

Results

Visual acuity (18 months)

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

Number of injections

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

Notes

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using random numbers tables, 60 numbers were randomly picked up from 1 to 120 and assigned to group A while the remaining sixty numbers were assigned to group B."
Allocation concealment (selection bias)	Unclear risk	"...randomization of the 120 numbers into two groups was done before initiation of enrolment itself. Upon initiation of enrollment, the patients were numbered sequentially based on the serial order of enrolment in the study. Depending on the enrolment number, the patients were

		automatically assigned to either group A or B based on the prior randomization of number 1-120 into two equal groups using random number tables."
Masking of participants (performance bias)	Unclear risk	Masking of participants not reported.
Masking of study personnel (performance bias)	Low risk	“The injections were given...by the investigators, who were blinded to the type of injection."
Masking of outcome assessment (detection bias)	Low risk	"All assessors were masked to the group of patient they were following up."
Incomplete outcome data (attrition bias)	Unclear risk	Sixteen (13%) participants lost to follow up were excluded from the analyses; 10 in the bevacizumab group and 6 in the ranibizumab group.
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial registration was identified for this study. Outcomes were reported for stated outcomes in the methods section of the published report; however, only P values were reported for between-group comparisons and no standard deviation or variance measures were reported for continuous outcomes.
Other bias	Low risk	None observed

Bibliographic reference	**CATT 2011** CATT Research Group; Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2011;364(20):1897-908.
Methods	**Number randomized (total and per group):** 1208 participants randomly assigned to study treatment; number of participants randomized per group not reported **Exclusions after randomization**: one study center (23 participants) was excluded due to protocol violations **Number analyzed (total and per group):** 1105 total participants; 265 in bevacizumab monthly group, 284 in ranibizumab monthly group, 271 in bevacizumab as needed group, and 285 in ranibizumab as needed group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 80 total participants: 21 in bevacizumab monthly group (4 died and 17 with missing data), 17 in ranibizumab monthly group (4 died and 13 with missing data), 29 in bevacizumab as needed group (11 died and 18 with missing data), 13 in ranibizumab as needed group (5 died and 8 with missing data)

	Compliance: limited information given: mean of 11.9 treatments given for bevacizumab monthly group and mean of 11.7 treatments given for ranibizumab monthly group **Intention to treat analysis**: no, 103 participants enrolled and randomized were not included in the analyses **Reported power calculation:** yes, sample of 277 participants per group for power of 90% **Study design comment:** non-inferiority design, four arms, six pairwise comparisons planned; at one year, participants in the monthly dose treatment groups were re-randomized to either continue with monthly injections or switch to as needed injections of the same treatment drug
Participants	**Country**: USA **Age**: mean was 80 years in bevacizumab monthly group, 79 years in ranibizumab monthly group, 79 years in bevacizumab as needed group, and 78 years in ranibizumab as needed group **Gender (percent):** 732/1185 (61.8%) women and 453/1185 (38.2%) men **Inclusion criteria**: age 50 years or older; one study eye per participant with untreated active CNV due to AMD (based on presence of leakage as seen by fluorescein angiography and of fluid as seen by OCT); VA of 20/25 to 20/320 on electronic visual-acuity testing **Exclusion criteria**: fibrosis or atrophy in center of fovea in the study eye; CNV in either eye due to other causes; retinal pigment epithelial tear involving the macula; any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention or contribute to VA loss during the 3 year follow-up period; active or recent (within 4 weeks) intraocular inflammation; current vitreous hemorrhage in the study eye; history of rhegmatogenous retinal detachment or macular hole; active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis; spherical equivalent > 8 diopters; intraocular surgery (including cataract surgery) in the study eye within 2 months; uncontrolled glaucoma; participants unable to be photographed to document CNV due to known allergy to fluorescein dye, lack of venous access or cataract obscuring the CNV; premenopausal women not using adequate contraception; pregnancy or lactation; history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications; current treatment for active systemic infection; uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders; history of recurrent significant infections or bacterial infections; inability to comply with study or follow-up procedures

<table>
<tr><td></td><td>Equivalence of baseline characteristics: a slightly higher percentage of participants in bevacizumab monthly group had history of transient ischemic attack (8.7% compared with 4% in ranibizumab monthly group, 4% in ranibizumab as needed group, and 6.3% in bevacizumab as needed group)
Diagnoses in participants: 688/1185 (58%) had active neovascular AMD with CNV in foveal center; 315/1185 (27%) had fluid in foveal center; 93/1185 (8%) had hemorrhage in foveal center; 71/1185 (6%) had other foveal center involvement; and 18/1185 (1.5%) had no CNV or not possible to grade</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg per 0.05 ml intravitreal bevacizumab injections on a fixed schedule of every 4 weeks for 1 year, at 1 year, re-randomization to bevacizumab every 4 weeks or as needed
Intervention 2: 0.5 mg intravitreal ranibizumab injections on a fixed schedule of every 4 weeks for 1 year, at 1 year, re-randomization to ranibizumab every 4 weeks or as needed
Intervention 3: 1.25 mg intravitreal bevacizumab as needed for 2 years
Intervention 4: 0.5 mg intravitreal ranibizumab as needed for 2 years
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention3</th><th>Intervention4</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Ranibizumab</td><td>Bevacizumab</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks for 1 year, re-randomization to bevacizumab every 4 weeks or as needed</td><td>Every 4 weeks for 1 year, re-randomization to ranibizumab every 4 weeks or as needed</td><td>As needed for 2 years</td><td>As needed for 2 years</td></tr>
</table>
Length of follow up:
Planned: 12 months for primary analysis; 24 months for secondary analyses, with modifications to two intervention arms as described above
Actual: 12 months for primary analysis; 24 months for secondary analyses</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: change in visual acuity from baseline at 12 months with a non-inferiority margin of 5 letters</td></tr>
</table>

Secondary outcomes: proportion of eyes with 15-letter change, number of injections, OCT measured change in foveal thickness, change in lesion size on OCT and also on fluorescein angiography, incidence of ocular and systemic adverse events, and annual drug cost

Intervals at which outcomes were assessed: weeks 4, 12, 24, 36, 52 during first year for visual acuity; weeks 4, 8, 12, 24, 52 for changes on OCT

Results

Visual acuity (12 months)

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

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

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

Adverse event after enrolment (12 months)

	Bevacizumab PRN (n=300)	Ranibizumab PRN (n=298)	Bevacizumab monthly (n=286)	Ranibizumab monthly (n=301)
Endophthalmitis	0	0	4 (1.4)	2 (0.7)

Death any cause	11 (3.7)	5 (1.7)	4 (1.4)	4 (1.3)
Nonfatal myocardial infarction	1 (0.3)	3 (1.0)	2 (0.7)	2 (0.7)
Nonfatal stroke	2 (0.7)	1 (0.3)	2 (0.7)	2 (0.7)
Cardiac disorder	13 (4.3)	12 (4.0)	16 (5.60)	10 (3.3)
Infection	18 (6.0)	12 (4.0)	11 (3.8)	6 (2.0)
Gastrointenstinal disorder	9 (3.0)	2 (0.7)	6 (2.1)	3 (1.0)
1 or more serious systemic event	77 (25.7)	61 (20.5)	64 (22.4)	53 (17.6)

Adverse event within 2 years of enrolment

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

Number of injections (one year)

	Bevacizumab PRN (n=300)	Ranibizumab PRN (n=298)	MD (95%CI)

Mean number of injections (SD)	7.7 (3.5)	6.9 (3.0)	0.80 (0.28, 1.32)

Notes	**Full study name**: Comparison of Age-related macular degeneration Treatment Trials **Type of study**: published **Funding**: National Eye Institute, National Institutes of Health, US **Declarations of interest**: one investigator reported receiving consulting fees from GlaxoSmithKline and another consulting fees from Neurotech and SurModics

	Study period: accrual February 2008 through December 2009; follow up through December 2011 **Reported subgroup analyses**: none, but risk factors for 2-year VA outcomes have been reported (Ying 2015 under CATT 2011) **Contacting study investigators**: trial authors not contacted as data were available in published reports

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

Bibliographic reference	**GEFAL 2013**

	Kodjikian L, Souied EH, Mimoun G, Mauget-Faysse M, Behar-Cohen F, Decullier E, et al. Ranibizumab versus bevacizumab for neovascular age-related macular degeneration: Results from the GEFAL noninferiority randomized trial. Ophthalmology 2013;120(11):2300-9.
Methods	**Number randomized (total and per group**): 501 participants randomly assigned to study treatment; 255 in bevacizumab group and 246 in ranibizumab group **Exclusions after randomization:** 16 participants excluded because they received no injection (9 in bevacizumab group and 7 in ranibizumab group) **Number analyzed (total and per group):** 485 participants (246 in bevacizumab group and 239 in ranibizumab group) for safety analysis at one year; 404 participants (207 in bevacizumab group and 197 in ranibizumab group) for analysis on visual acuity at one year; most data analyzed for 374 participants (191 in bevacizumab group and 183 in ranibizumab group) with available baseline BCVA data, at least 10 months follow up, and did not have major deviations from the study protocol **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 81 total participants: 39 in bevacizumab group and 42 in ranibizumab group; additional 30 participants (16 in bevacizumab group and 14 in ranibizumab group) excluded from most analyses due to protocol violations **Compliance**: 374/501 participants completed the study without major protocol violations **Intention to treat analysis**: no, not all participants enrolled and randomized were included in the analyses **Reported power calculation**: yes, sample of 200 participants per group for power of 90% to detect 15 letters changes in BCVA **Study design comment:** non-inferiority design
Participants	**Country**: France (38 study centers) **Age**: mean age for 374 participants without major protocol violations was 79 years **Gender (percent**): 248/374 (66%) women and 126/374 (34%) men **Inclusion criteria**: age 50 years or older; active subfoveal neovascular AMD (one study eye eligible in bilateral cases); lesion size < 12 disk areas; recent development of lesion in cases of occult neovessels; BCVA of 20/32 to 20/320 on ETDRS scale **Exclusion criteria**: subretinal hemorrhage reaching foveal center and > 50% of the lesion area; fibrosis or atrophy in center of fovea in the study eye; CNV of other pathogenesis; retinal pigment epithelial tear reaching the macula; previous or current treatment with intravitreal anti-VEGF therapy; history of treatment 3 months prior or intraocular surgery 2

<table>
<tr><td></td><td>months prior to first study injection; history of photocoagulation or intravitreal medical device in the study eye; ocular or periocular infection; intraocular inflammation; diabetic retinopathy; history of autoimmune or idiopathic uveitis; IOP ? 25 mmHg with topical hypotensive therapy; aphakia or lack of lens capsule in the study eye; known illness or condition requiring intraocular surgery within 12 months; known hypersensitivity to study drugs or allergy to agents used for ocular testing; uncontrolled arterial hypertension; history of treatment with systemic bevacizumab; premenopausal women not using adequate contraception; involvement in another clinical study; not part of French national health insurance program
Equivalence of baseline characteristics: yes
Diagnoses in participants: 354/374 (95%) had intraretinal and/or subretinal fluid on OCT</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg in 0.05 ml intravitreal bevacizumab injections every month for first three months; re-treatment afterwards based on OCT or VA changes
Intervention 2: 0.50 mg intravitreal ranibizumab injections every month for first three months; re-treatment afterwards based on OCT or VA changes
<table>
<tr><th></th><th>Intervention1</th><th>Intervention2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Monthly for 3 months</td><td>Monthly for 3 months</td></tr>
<tr><td></td><td colspan="2">Retreatment after initial 3 doses afterwards based on OCT or VA changes</td></tr>
</table>
Length of follow up: Planned: 1 year; Actual: 1 year</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: mean change in BCVA at 1 year (at least 10 months after inclusion), as measured on an ETDRS chart
Secondary outcomes, as defined in published reports: visual acuity outcomes at 1 year: BCVA, change in BCVA, proportion with gain of ≥15 letters, proportion with loss of ≥15 letters, proportion with gain of ≥5 letters, proportion with loss of ≥5 letters; change in CNV area between the baseline and final evaluations; presence of intraretinal and/or subretinal fluid; presence of pigment epithelial detachment; central subfield macular thickness; change in central subfield macular thickness; dye leakage on angiogram; number of injections; model of OCT equipment; adverse events</td></tr>
</table>

	Secondary outcomes, as defined in trial registry: efficacy of treatments at 1 year; proportions of ocular and systemic adverse events at 1 year; average number of injections and time before re-injection during 1 year; drug profiles in blood and aqueous humor of a subset of 20 participants at 3 months; medico-economic impact of treatments at 1 year **Intervals at which outcomes were assessed**: monthly through 12 months

Results

Visual acuity (12 months)

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

Adverse events (12 months)

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

Number of injections (12 months)

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

Notes

Full study name: Groupe d'Etude Français Avastin versus Lucentis dans la DMLA néovasculaire

	Type of study: published **Funding sources**: French Ministry of Health (Programme Hospitalier de Recherche Clinique National 2008); the French Health Insurance System co-financed the study and funded study drugs **Declarations of interest**: four authors declared disclosures as principal investigators for trials sponsored by Novartis, Bausch & Lomb, Théa, and Alcon; serving on advisory boards for Alcon, Allergan, Bayer, Bausch & Lomb, Novartis, and Théa; receiving lecture fees from Alcon, Allergan, Bayer, Bausch & Lomb, Heidelberg Engineering, the Krys group, Novartis, Théa, and Zeiss; receiving consulting fees from Novartis, Bayer, and Allergan; or receiving honoraria from Novartis, Bayer, and Allergan; the other four authors declared no conflicts of interests **Study period**: random enrollment 24 June 2009 to 9 November 2011 **Reported subgroup analyses**: none **Contacting study investigators**: trial authors contacted and contributed information for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization was stratified by center and visual acuity (threshold: 20/100). Local hospital pharmacies were responsible for randomizing patients in each center using pre-established lists.'"
Allocation concealment (selection bias)	Low risk	Hospital pharmacy used to conceal treatment assignments prior to participant enrollment and randomization (email communication with Dr Kodjikian, dated 7 August 2014).
Masking of participants (performance bias)	Low risk	"Identical syringes were masked and delivered by local hospital pharmacies after aseptic preparation in authorized, centralized drug-preparation units, using vials of Avastin 100 mg/ml and Lucentis 10 mg/ml." "The main strength of the GEFAL trial is that the study remained effectively double-masked, unlike CATT in which some participants received billing information and IVAN in which the masking differed between centers (some treating teams were aware of treatment allocation)."
Masking of study personnel (performance bias)	Low risk	"Identical syringes were masked and delivered by local hospital pharmacies after aseptic preparation in authorized, centralized drug-preparation units, using vials of Avastin 100 mg/ml and Lucentis 10 mg/ml." "The main strength of the GEFAL trial is that the study remained effectively double-masked, unlike CATT in which some participants received billing information and IVAN in which the masking differed between centers (some treating teams were aware of treatment allocation)."

Masking of outcome assessment (detection bias)	Low risk	Only the pharmacists who prepared the syringes knew about the randomization assignments; ophthalmologists, study coordinators, and all outcome assessors were masked like participants (email communication with Dr Kodjikian, dated 7 August 2014).
Incomplete outcome data (attrition bias)	Unclear risk	16/501 (3%) participants randomized were not included in any analysis; most analyses reported did not include 127/501 (25%) of participants.
Selective reporting (reporting bias)	Unclear risk	Differences in outcomes between the trial registration and published one-year results papers included: 1) secondary visual acuity and morphology outcomes were specified clearly in the paper, but described only as 'efficacy of treatments' in the trial registration;2) the published paper included model of OCT equipment as outcome, whereas the trial registration did not; and 3) the trial registration included time before re-injection during one year, drug profiles in blood and aqueous humor of a subset of 20 participants at 3 months, and medico-economic impact of treatments as outcomes, whereas the published paper did not.
Other bias	Low risk	None observed

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

	Number analyzed (total and per group): at one year follow up: 561 total participants at one year; 136 in continued bevacizumab group; 138 in discontinued bevacizumab group; 141 in continued ranibizumab group; and 146 in discontinued ranibizumab group at two years follow up: 525 total participants at one year; 127 in continued bevacizumab group; 127 in discontinued bevacizumab group; 134 in continued ranibizumab group; and 137 in discontinued ranibizumab group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up:** at one year follow up: 49 total participants: 4 participants receiving treatment withdrew prior to completing third injection (2 in bevacizumab group and 2 in ranibizumab group); 45 participants randomized to regimen groups exited trial before one year (13 in continued bevacizumab group; 7 in discontinued bevacizumab group; 16 in continued ranibizumab group; and 9 in discontinued ranibizumab group) at two years follow up: 85 total participants: 5 participants receiving treatment withdrew prior to completing third injection (3 in bevacizumab group and 2 in ranibizumab group); 80 participants randomized to regimen groups exited trial before two years (21 in continued bevacizumab group; 18 in discontinued bevacizumab group; 23 in continued ranibizumab group; and 18 in discontinued ranibizumab group) **Compliance**: the wrong study drug was administered twice during the first year; at one year follow up: adherence was 6576/6699 (98%) scheduled injections received at two years follow up: adherence was 12761/14640 (87%) scheduled injections received **Intention to treat analysis**: no, 67 participants enrolled and randomized were not included in the analyses at one year and 103 at two years **Reported power calculation**: yes, sample of 600 participants per group for power of 90% to detect non-inferiority **Study design comment**: non-inferiority design; 2 x 2 factorial design – randomization in two stages: first randomized to drug treatment (bevacizumab or ranibizumab), then to treatment regimen (continue monthly injections or discontinue monthly injections and switch to as needed injections given in three month cycles); results reported only as bevacizumab versus ranibizumab and continuous versus discontinuous
Participants	**Country**: UK (23 study centers) **Age**: mean age for 610 participants receiving treatment was 78 years **Gender (percent):** 366/610 (60%) women and 244/610 (40%) men **Inclusion criteria**: age 50 years or older; previously untreated neovascular AMD in study eye with any component of the neovascular lesion (CNV, blood, serous pigment epithelial detachment, elevated blocked fluorescence) involving the

<table>
<tr><td></td><td>center of the fovea, confirmed by fluorescein angiography; best-corrected VA of 25 letters or greater on the ETDRS chart (measured at 1 m)
Exclusion criteria: neovascular lesion of 50% or more fibrosis or blood; more than 12 disc diameters; argon laser treatment in study eye within 6 months; presence of thick blood involving the center of the fovea; presence of other active ocular disease causing concurrent vision loss; myopia 8 or more diopters; previous treatment with PDT or a VEGF inhibitor in study eye; women pregnant, lactating, or of child-bearing potential; men with a spouse or partner of child-bearing potential
Equivalence of baseline characteristics: yes
Diagnoses in participants: 301/610 (58%) had neovascular AMD with CNV in foveal center; 308/610 (54%) had fluid in foveal center; 90/610 (16%) had hemorrhage in foveal center; 75/610 (13%) had other foveal center involvement; and 15/610 (3%) had no CNV or not possible to grade</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg in 0.05 ml intravitreal bevacizumab injected monthly for two years
Intervention 2: 0.5 mg intravitreal ranibizumab injected monthly for two years
Intervention 3: after first 3 monthly 1.25 mg intravitreal bevacizumab injections, monthly treatment was discontinued and treatment was given as needed in cycles of 3 monthly doses
Intervention 4: after first 3 monthly 0.5 mg intravitreal ranibizumab injections, monthly treatment was discontinued and treatment was given as needed in cycles of 3 monthly doses
<table>
<tr><td></td><td>Intervention1</td><td>Intervention2</td><td>Intervention3</td><td>Intervention4</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td colspan="2">Monthly for 2 years
Monthly for 2 years</td><td colspan="2">Initial 3 doses monthly, then treatment was givens as needed in cycles of 3 monthly dosee</td></tr>
</table>
Follow up: Planned length: 2 years; Actual length: 2 years
Frequency of follow-up assessments: monthly</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: best-corrected distance visual acuity measured as ETDRS letters at two years
Secondary outcomes, as defined in protocol: at 1 year and 2 years follow up - frequencies of adverse effects of treatment; generic and vision-specific health-related quality of life; treatment satisfaction; cumulative resource use/cost</td></tr>
</table>

and cost-effectiveness; clinical measures of vision (contrast sensitivity measured with Pelli-Robson charts, near visual acuity measured by Bailey-Love near reading cards, and reading speed measured with Belfast reading charts); lesion morphology (fluorescein angiography and OCT); distance visual acuity at one year; survival free from treatment failure
Exploratory analysis: association between serum markers and cardiovascular serious adverse events
Intervals at which outcomes were assessed: monthly through 24 months; various data were collected at every visit depending on assessment schedule and regimen group

Results

Visual acuity (12 months)

	Bevacizumab monthly (n=134)	Bevacizumab PRN (n=136)	Ranibizumab monthly (n=140)	Ranibizumab PRN (n=143)
Gain of ≥ 15 letters, no.	19	25	36	29
Loss of ≥15 letters	7	5	6	6
Gain or loss less than 15 letters	108	106	98	108
BCVA, letters (SD)	4.4 (13.2)	5.1 (11.4)	7.8 (14.2)	5.1 (10.4)

Visual acuity (24 months)

	Bevacizumab monthly (n=126)	Bevacizumab PRN (n=123)	Ranibizumab monthly (n=133)	Ranibizumab PRN (n=135)
Gain of ≥ 15 letters, no.	24	17	41	22
Loss of ≥15 letters	12	11	8	15
Gain or loss less than 15 letters	90	95	84	98
BCVA, letters (SD)	3.6 (15.2)	4.5 (11.5)	7.3 (15.2)	2.6 (14.4)

Notes

Full study name: alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation
Type of study: published
Funding sources: National Institute for Health Research Health Technology Assessment program, UK

	Declarations of interest: various authors reported being principal investigators of trials sponsored by Novartis; attending and being remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan, and/or Bausch and Lomb; being employed by institution that has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and/or Pfizer; receiving honoraria from Novartis for lecture and/or teaching fees from Janssen-Cilag **Study period**: random enrollment 27 March 2008 to 15 October 2010 **Reported subgroup analyses:** 3 genetic polymorphisms (Lotery 2013) **Contacting study investigators**: trial authors not contacted as data were available in published reports

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomized allocations were computer generated by a third party in blocks and stratified by center." "Randomisation was stratified by centre and was blocked to ensure roughly equal numbers of participants per group within a centre."
Allocation concealment (selection bias)	Low risk	"Research teams at sites recruited participants, and accessed a password-protected website to randomize participants. Allocations were concealed until participants' eligibility and identities were confirmed." "Allocations were computer generated and concealed with an internet-based system (Sealed Envelope, London, UK). Staff in participating centres accessed the website and, on entering information to confirm a participant's identity and eligibility, were provided with the unique study number."
Masking of participants (performance bias)	Low risk	From study protocol: "Participants, clinicians and trial personnel will be masked to the VEGF inhibitor to which a participant is assigned." "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Masking of study personnel (performance bias)	Low risk	"We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments."

		From study protocol:"We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Masking of outcome assessment (detection bias)	Low risk	"We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments." From study protocol: "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Incomplete outcome data (attrition bias)	Unclear risk	67/628 (11%) participants randomized were not included in the one-year analysis; 111/628 (18%) participants randomized were not included in the two-year analysis.
Selective reporting (reporting bias)	Unclear risk	Differences between the protocol and published one-year and two-year results papers included: 1) two secondary outcomes in the protocol were not listed in paper: treatment satisfaction and survival free from treatment failure; and 2) exploratory (serum) analysis in protocol upgraded to a secondary outcome in paper.
Other bias	Low risk	None observed

Bibliographic reference	**LUCAS 2015** Berg K, Pedersen TR, Sandvik L, Bragadottir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and extend protocol. Ophthalmology 2015;122(1):146-52
Methods	**Number randomized (total and per group):** 441 participants randomly assigned to study treatment; 220 in bevacizumab group and 221 in ranibizumab group **Exclusions after randomization**: 10 total participants; 7 in the bevacizumab group and 3 in the ranibizumab group. "All 9 patients from 1 study center were excluded becasue of serious protocol violations, and 1 patient was excluded after a serious retinal and viteous hemmorhage . . . " **Number analyzed (total and per group**): 371 total participants; 184 in bevacizumab group and 187 in ranibizumab group **Unit of analysis:** individuals (one study eye per participant) **Losses to follow up**: none, but 60 excluded from analysis (29 in the bevacizumab group and 31 in the ranibizumab group), including 11 total participants who died

<table>
<tr><td></td><td>Compliance: 371/441 participants completed the study per protocol
Intention to treat analysis: no, 70 participants enrolled and randomized were not included in analysis
Reported power calculation: yes, 181 participants per arm to provide 80% power to detect or rule out a difference in visual acuity outcome, assuming a 10% dropout rate
Study design comment: non-inferiority design using margin of 5 letters on ETDRS chart</td></tr>
<tr><td>Participants</td><td>Country: 10 clinical centers in Norway
Age: mean 78.7 years in bevacizumab group and 78.0 in ranibizumab group
Gender (percent): 140/431 (32.5%) men and 291/431 (67.5%) women
Inclusion criteria: age 50 years or older; previously untreated active neovascular AMD in study eye; BCVA in study eye between 20/25 and 20/120, measured at 4 meters using an ETDRS "standardized viewer"
Exclusion criteria: "Pigment epithelial detachments with no associated intraretinal or subretinal edema and lesions comprising more than 50% blood or fibrosis were excluded."
Equivalence of baseline characteristics: more participants in the ranibizumab group had a history of myocardial infarction
Diagnoses in participants: neovascular AMD; 86% had CNV under the foveal center</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg per 0.05 ml intravitreal bevacizumab injections every 4 weeks until no signs of active AMD were found based on OCT and biomicroscopic fundus examination, followed by the "treat and extend" protocol
Intervention 2: 0.5 mg intravitreal ranibizumab injections every 4 weeks, followed by the "treat and extend" protocol
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks until no signs of active AMD (based on OCT), followed by treat and extend protocol</td><td>Every 4 weeks, followed by the treat and extended protocol</td></tr>
</table>
The "treat and extend" protocol for each treatment group specified that whenever a new injection was given, the "period" (interval) to the next injection was to be extended by 2 weeks up to a maximum interval of 12 weeks. Whenever</td></tr>
</table>

<table>
<tr><td></td><td>recurrent neovascularization was treated, the interval was shortened by 2 weeks until the lesion was inactive. Interval extension was then restarted to a maximum of 2 weeks less than when the recurrence was observed,
Follow up: Planned length: 24 months; Actual length: 12 months
Frequency of follow-up assessments: 4-week intervals, modified by 2-week increases or decreases, as described above</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: "change in BCVA at 1 year as measured on the ETDRS visual acuity chart"
Secondary outcomes, as defined: "number of injections, change in CRT as measured with OCT, and change in lesion size as measured on FA"
Safety outcome: occurrence of arteriothrombotic events
Intervals at which outcomes were assessed: unclear, but presumably whenever participant was assessed for the need for retreatment</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)
<table>
<tr><td></td><td>Bevacizumab (n=184)</td><td>Ranibizumab (n=187)</td><td>RR (95%CI)</td></tr>
<tr><td>Gain of ≥ 15 letters, n (%)</td><td>47 (25.5)</td><td>50 (26.7)</td><td>0.96 (0.68, 1.35)</td></tr>
<tr><td>Loss of ≥ 15 letters</td><td>7 (3.8)</td><td>8 (4.3)</td><td>0.89 (0.33, 2.40)</td></tr>
<tr><td>Gain or loss of less than 15 letters</td><td>130</td><td>129</td><td>1.02 (0.90, 1.17)</td></tr>
</table>
Adverse event within 1 year of recruitment (12 months)
<table>
<tr><td></td><td>Bevacizumab (n=220)</td><td>Ranibizumab (n=221)</td><td>RR (95%CI)</td></tr>
<tr><td>Macular haemorrhage</td><td>2</td><td>0</td><td>5.02 (0.24, 104.02)</td></tr>
<tr><td>Death any cause</td><td>4</td><td>7</td><td>0.57 (0.17, 1.93)</td></tr>
<tr><td>Nonfatal myocardial infarction</td><td>0</td><td>6</td><td>0.08 (0.00, 1.36)</td></tr>
<tr><td>Nonfatal stroke</td><td>2</td><td>3</td><td>0.67 (0.11, 3.97)</td></tr>
<tr><td>Cardiac disorder</td><td>5</td><td>14</td><td>0.36 (0.13, 0.98)</td></tr>
<tr><td>Infection</td><td>4</td><td>5</td><td>0.80 (0.22, 2.95)</td></tr>
<tr><td>Gastrointestinal disorder</td><td>5</td><td>5</td><td>1.00 (0.29, 3.42)</td></tr>
</table></td></tr>
</table>

	≥1serious systematic event	37	45	0.83 (0.56, 1.22)

Number of injections (12 months)

	Bevacizumab (n=184)	Ranibizumab (n=187)	MD (95%CI)
Mean number of injections (SD)	8.9 (2.6)	8.0 (2.3)	0.90 (0.40, 1.40)

Notes

Full study name: Lucentic Compared to Avastin Study
Type of study: published
Funding sources: Oslo University Hospital, Oslo, Norway
Declarations of interest: "The funding organization had no role in the design of the study but aided in the conduct of the study and data management." One author had participated in an advisory board meeting for another anti-VEGF agent for Bayer.
Study period: random enrolment March 2009 to July 2012
Reported subgroup analyses: none
Contacting study investigators: pending

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated by a third party at the Norwegian University of Science and Technology, Trondheim . . . with the use of the block method and stratification by centre."
Allocation concealment (selection bias)	Low risk	The drugs were allocated by unmasked study nurses who were also responsible for aseptic filling of a syringe with the assigned study drug. The identical syringes, regardless of which drug was given, were filled by these nurses behind a screen. The syringe was then presented directly to the treating ophthalmologist."
Masking of participants (performance bias)	Low risk	"the patient, the treating ophthalmologist, and the assisting nurse were masked to the drug at all times."
Masking of study personnel (performance bias)	Low risk	"These study nurses were not involved in any other patient-related activities in the study."

Masking of outcome assessment (detection bias)	Low risk	"Ophthalmic nurses, who also were masked to the drug and patient records, tested the ETDRS visual acuity."
Incomplete outcome data (attrition bias)	Unclear risk	About 15% of participants were missing 12-month outcome data, compared to 10% assumed in sample size calculation.
Selective reporting (reporting bias)	Low risk	All outcomes specified were reported.
Other bias	Low risk	No other bias identified

Bibliographic reference	**MANTA 2013** Krebs I, Schmetterer L, Boltz A, Told R, Vécsei-Marlovits V, Egger S, et al. A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration. British Journal of Ophthalmology 2013;97(3):266-71.
Methods	**Number randomized (total and per group):** 321 participants randomly assigned to study treatment; number per group not reported **Exclusions after randomization**: 4 participants (3 due to receiving the wrong drug and 1 because the participant received prior treatment and was not eligible) **Number analyzed (total and per group):** 317 total participants; 154 in bevacizumab group and 163 in ranibizumab group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 69 participants: reasons for losses to follow up not reported (33 in bevacizumab group, 36 in ranibizumab group) **Compliance**: 248/317 participants completed the study **Intention to treat analysis:** no, 4 participants enrolled and randomized were not included in analysis; data imputed using last-observation-carried-forward method for 69 participants lost to follow up **Reported power calculation:** yes, sample of 320 participants for power of 95% **Study design comment:** non-inferiority design
Participants	**Country:** 10 clinical centers in Austria **Age**: mean 76.7 years in bevacizumab group and 77.6 years in ranibizumab group **Gender** (percent): 115/317 (36.3%) men and 202/317 (63.7%) women

<table>
<tr><td></td><td>Inclusion criteria: age 50 years or older; active primary or recurrent subfoveal lesion with CNV, measured by fluorescein angiography or OCT; BCVA in study eye between 20/40 to 20/320, measured by ETDRS charts
Exclusion criteria: previous treatment for CNV or AMD; prior treatment with any intravitreal drug or verteporfin PDT in study eye; prior treatment with systemic bevacizumab; prior treatment with any intravitreal drug or verteporfin PDT in non-study eye within 3 months; laser photocoagulation in study eye within 1 month; participation in another clinical trial within 1 month; subfoveal fibrosis or atrophy > 50% in study eye; CNV in either eye due other causes than AMD; RPE tear involving macula of study eye; history of uncontrolled glaucoma or concurrent intraocular condition in study eye; pregnancy; allergy to fluorescein; inability to comply with study procedures
Equivalence of baseline characteristics: yes
Diagnoses in participants: active primary or recurrent subfoveal CNV</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg per 0.05 ml intravitreal bevacizumab injections every month for first three months; re-treatment afterwards based on OCT or VA changes
Intervention 2: 0.5 mg intravitreal ranibizumab injections every month for first three months; re-treatment afterwards based on OCT or VA changes
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Monthly for 3 months; retreatment based on OCT or VA changes</td><td>Monthly for 3 months, retreatment based on OCT or VA changes</td></tr>
</table>
Length of follow up: Planned: 12 months; Actual: 12 months</td></tr>
<tr><td>Outcomes</td><td>Primary outcomes, as defined: "mean change in BCVA between baseline and 1 year"
Secondary outcomes, as reported: Kaplan-Meier proportions of the gain of 15 letters of vision, gain of 5 letters of vision, loss of 5 letters of vision, loss of 15 letters of vision; lesion size, assessed by fluorescein angiography; number of retreatments; and retinal thickness, assessed by OCT
Adverse events
Intervals at which outcome assessed: monthly through 12 months</td></tr>
</table>

Results

Visual acuity (12 months)

	Bevacizumab (n=154)	Ranibizumab (n=163)	RR (95%CI)
Gain of ≥15 letters, n	36	35	1.09 (0.72, 1.64)
Loss of ≥15 letters	8	10	0.85 (0.34, 2.09)
Gain or loss less than 15 letters	110	118	0.99 (0.86, 1.13)

Adverse event (12 months)

	Bevacizumab (n=154)	Ranibizumab (n=163)	RR (95%CI)
Total no. of patients reported AE	19	15	1.34 (0.71, 2.54)
Death	3	2	1.59 (0.27, 9.37)
Vascular disorder	5	3	1.76 (0.43, 7.26)
Infection	3	3	1.06 (0.22, 5.16)

Number of re-treatment (12 months)

	Bevacizumab (n=154)	Ranibizumab (n=163)	MD (95%CI)
Mean number (SD)	6.1 (2.8)	5.8 (2.7)	0.30 (-0.31, 0.91)
During the observation, 6 patients required treatment also in the fellow eye (4 in the ranibizumab group, 2 in the bevacizumab group).			

Notes

Full study name: A Randomized Observer and Subject Masked Trial Comparing the Visual Outcome After Treatment With Ranibizumab or Bevacizumab in Patients With Neovascular Age-related Macular Degeneration Multicenter Anti VEGF Trial in Austria
Type of study: published
Funding sources: Austrian ophthalmologic society; the Ludwig Boltzmann Institute of Retinology and Biomicroscopic Lasersurgery; the participating study center sitesDeclarations of interest: authors reported no competing interests
Study period: not reported
Reported subgroup analyses: none

	Contacting study investigators: trial authors contacted; no additional information provided for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was stratified according to the clinical centre using a permuted block method with a fixed block size of 20."
Allocation concealment (selection bias)	Low risk	"Eligible patients were randomized in a 1:1 ratio to one of two groups by members of the Department of Clinical Pharmacology, Medical University of Vienna, which was otherwise not involved in the study.
Masking of participants (performance bias)	Low risk	"All other personnel and the patients were masked to treatment assignment."
Masking of study personnel (performance bias)	Low risk	"The evaluating physician was masked to treatment assignment, whereas the injecting physician was not involved in the collection of data."
Masking of outcome assessment (detection bias)	Low risk	"The evaluating physician was masked to treatment assignment, whereas the injecting physician was not involved in the collection of data."
Incomplete outcome data (attrition bias)	Unclear risk	There were 4/321 (1.2%) participants excluded from the study. At 12 months, 69 participants did not have outcome data; last-observation-carried-forward method was used to impute missing data for these 69 participants.
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes were reported.
Other bias	Low risk	None observed

The BRAMD study described below was identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

Bibliographic reference	**Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016**
Country/ies	Netherlands
Study type	RCT

Bibliographic reference	**Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016**
Aim of the study	To compare the effectiveness of bevacizumab and ranibizumab in the treatment of exudative age-related macular degeneration (AMD). Design: Multicentre, randomized, controlled, double-masked clinical trial in 327 patients.
Study dates	Published 2016
Sources of funding	This study was funded by the Netherlands organisation for health research and development. This study was supported by Dutch health insurance companies.
Sample size	327
Inclusion Criteria	Patients 60 years of age or higher. Patients with primary or recurrent sub-, juxta- or extrafoveal CNV secondary to AMD, including those with RAP, that may benefit from anti-VEGF treatment in the opinion of the investigator. Patients with primary or recurrent sub-, juxta- or extrafoveal CNV secondary to AMD, including those with RAP, that may benefit from anti-VEGF treatment in the opinion of the investigator. The total area of CNV (including both classic and occult components) encompassed within the lesion must be more or equal to 30% of the total lesion area. The total lesion area should be < 12 disc areas. A best corrected visual acuity (BCVA) score between 78 and 20 letters (approximately 0,63–0,05 Snellen equivalent) in the study eye.
Exclusion Criteria	Ocular treatment with anti-angiogenic drugs in the last 2 months or Triamcinolone in the last 6 months. Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within one month preceding Baseline. Patients with angioid streaks or precursors of CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia. Spherical equivalent of refractive error in the study eye demonstrating more than– 8 dioptres of myopia. Cataract extraction within three months preceding Baseline IOP >25 mm Hg Active intraocular inflammation in the study eye. Vitreous haemorrhage obscuring view of the posterior pole in the study eye. Presence of a retinal pigment epithelial tear involving the macula in the study eye. Subretinal haemorrhage in the study eye if the size of the haemorrhage is > 70% of the lesion

<table>
<tr><th>Bibliographic reference</th><td>Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016</td></tr>
<tr><td></td><td>Subfoveal fibrosis or atrophy in the study eye.
History of hypersensitivity or allergy to fluorescein.
Inability to obtain fundus photographs, fluorescein angiograms or OCT’s of sufficient quality to be analyzed and graded by the Central Reading Centre.
Systemic disease with a life expectancy shorter than the duration of the study.
Inability to adhere to the protocol with regard to injection and follow-up visits.
Legally incompetent adult
Refusal to give written informed consent</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Bevacizumab (n=161)</th><th>Ranibizumab (n=166)</th><th>All (n=327)</th></tr>
<tr><td>Mean age (SD)</td><td>79 (7)</td><td>78 (7)</td><td>78 (7)</td></tr>
<tr><td>Male: n (%)</td><td>72 (45%)</td><td>73 (44%)</td><td>145 (44%)</td></tr>
<tr><td>Caucasuan: n(%)</td><td>158 (98%)</td><td>163 (98%)</td><td>321 (98%)</td></tr>
<tr><td>Mean BCVA (SD)</td><td>60 (13)</td><td>60 (14)</td><td>60 (13)</td></tr>
<tr><td>BCVA≤52 letters: n (%)</td><td>42 (26%)</td><td>43 (26%)</td><td>85 (26%)</td></tr>
<tr><td>Active CNV: n(%)</td><td>161 (100%)</td><td>165 (99.9%)</td><td>326 (99.9%)</td></tr>
<tr><td>Predominiantly classic CNV, n(%)</td><td>44 (28%)</td><td>41 (26%)</td><td>85 (27%)</td></tr>
<tr><td>Minimally classic CNV: n (%)</td><td>18 (12%)</td><td>33 (21%)</td><td>51 (16%)</td></tr>
<tr><td>Occult CNV, n(%)</td><td>93 (60%)</td><td>84 (53%)</td><td>177 (57%)</td></tr>
<tr><td>EQ-5D state score (SD)</td><td>6.2 (1.2)</td><td>6.4 (1.3)</td><td>6.3 (1.3)</td></tr>
</table>
</td></tr>
<tr><td>Study visits and procedures</td><td>Participants were allocated to one of two study arms: monthly injections (window, 30 ± 7 days) with 1.25 mg of bevacizumab or with 0.5 mg ranibizumab.</td></tr>
</table>

Bibliographic reference	**Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016**
	The commercially available formulations of bevacizumab and ranibizumab were used and both were prepared for injection by aspiration in a Kendall monoject syringe in an aseptic manufacturing facility to ensure masking for everybody taking part in the study, apart from the pharmacists. Syringes were only labelled with the patient identification number. Prepared syringes were kept at 4°Celsius and injections were given not later than 24 hours after preparation. Participants attended monthly for a protocolized BCVA measurement, SD-OCT (3D and cross scans) and intravitreal injection with the allocated drug. Besides the identical syringes masking was also ensured by the fact that the ophthalmologists who performed the injections did not take part in interpretation of any data or patient assessment. The patient was labelled as a poor-responder and treatment was changed to the other drug, if at any visit after the third injection there was a drop in BCVA of more than 10 letters compared to baseline and there was clear evidence of active CNV or leakage by qualitative SD-OCT and/or FA assessment or at least two of the following signs of leakage on OCT; central retinal thickening >300 micron (CRT), intraretinal cysts or subretinal fluid any time after the third injection. The choice for CRT > 300 micron was based on the assumption that this would be more than two standard deviations above the mean CRT of a healthy retina in all three the devices used (see also below). FA and a standardized full ophthalmic examination were done at baseline, 4 months and exit visit.
Intervention	intravitreal bevacizumab 1.25mg monthly
Comparator	Intravitreal ranibizumab 0.5mg monthly
Outcomes	Primary outcome: Change in best-corrected visual acuity Secondary outcome: Proportoin of people with a loss of BCVA less than 15 letters from baseline at 12 months (responders) Proportion of patients with a loss or a gian of BCVA less than 15 letters from basedlin at 12 months (stabilizers) Proportion of people with 15 letters loss or more BCVA from baseline at 12 months (losers) Proportion of drpouts befire the final 12 months assessment Proportion of switcher after the third injection Adverse event
Analyses	Non-inferiority is assumed if the difference between both groups is 4 letters or less using a onesided t-test with a significance level of 0.05.

<table>
<tr><th>Bibliographic reference</th><td>Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016</td></tr>
<tr><td></td><td>We performed intention-to-treat (ITT) analysis. When patients did not complete the study, their last available BCVA-score was used as the BCVA-score at visit 14 (last-observation-carried-forward). Further, to minimize the risk of false claiming non-inferiority we used the BCVA at the moment of switch for patients who were switched to the other treatment.
The mean BCVA-change per treatment group was calculated.
Covariance analysis of the BCVA-change was used with treatment as fixed factor and baseline BCVA-score as covariate.</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Result</td><td>Visual acuity
<table>
<tr><th></th><th>Bevacizumab (n=161)</th><th>Ranibizumab (n=166)</th><th>Effect (95%CI)</th></tr>
<tr><td>Best-corrected visual acuity changes (ETDRS letter score), all patients</td><td>5.1 (14.1)</td><td>6.4 (12.2)</td><td>-1.30 (-4.16, 1.56)</td></tr>
<tr><td>Best-corrected visual acuity changes (ETDRS letter score), excluded patients switched the agents (n=17)</td><td>6.64 (12.8)</td><td>7.11 (11.6)</td><td>-0.47 (-3.12, 2.18)</td></tr>
<tr><td>Best-corrected visual acuity changes (ETDRS letter score), treatment naïve (n=284)</td><td>6.06 (13.67)</td><td>6.82 (12.63)</td><td>-0.76 (-3.82,2.30)</td></tr>
<tr><td>N, % of people had a gain of ≥15 letters</td><td>39, 24%</td><td>32, 19%</td><td>1.25 (0.83, 1.89)</td></tr>
<tr><td>N, % of people had a loss of ≥15 letters</td><td>18, 11%</td><td>8, 5%</td><td>2.31 (1.03, 5.15)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016

N, % of people had a loss or gain of <15 letters	105, 65%	126, 76%	0.85 (0.74, 0.98)
N, % of people drop out	34, 21%	28 (17%)	1.24 (0.79, 1.95)

Adverse event

	Bevacizumab (n=161)	Ranibizumab (n=166)	Effect (95%CI)
Occurance of SAEs	34	37	0.94 (0.62, 1.42)
1Death due to SAE	1	1	1.02 (0.06, 16.24)
Life-threathening conditions	1	2	0.51 (0.05, 5.60)
Hosptialisation	30	32	0.96 (0.61, 1.50)
Severe permanent damange	1	0	3.07 (0.13, 74.90)
No relation to study medication	32	35	0.94 (0.61, 1.44)
Improbable relation to study medication	1	1	1.02 (0.06, 16.24)
MedDRA system organ class			
Cardiact disorder	4	6	0.68 (0.20, 2.38)
Infection	4	4	1.02 (0.26, 4.03)
Nervous system disorder	3	1	3.07 (0.32, 29.25)

Bibliographic reference	Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016
	<table><tr><td>Injury or procedural complication</td><td>5</td><td>1</td><td>5.12 (0.61, 43.38)</td></tr><tr><td>Benigh or malignant neoplasm</td><td>2</td><td>3</td><td>0.68 (0.12, 4.03)</td></tr><tr><td>Surgerical or medical procedure</td><td>13</td><td>16</td><td>0.83 (0.41, 1.68)</td></tr><tr><td>Gastrointestinal disorder</td><td>2</td><td>2</td><td>1.02 (0.15, 7.19)</td></tr><tr><td>Any other system organ class</td><td>18</td><td>17</td><td>1.08 (0.58, 2.03)</td></tr></table>
Missing data handling/loss to follow up	21% patients in bevacizumab and 17% patients in ranibizumab dropped out in the study.
Was allocation adequately concealed?	The randomization list was imported into the data management system Oracle Clinical. Upon randomization of a patient, an automatized email notification containing the allocation result was sent to the site's pharmacy keeping the investigator and trial personnel blinded from treatment allocation.
Was knowledge of the allocated intervention adequately prevented during the study?	Upon randomization of a patient, an automatized email notification containing the allocation result was sent to the site's pharmacy keeping the investigator and trial personnel blinded from treatment allocation.
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes
Were incomplete outcome data adequately addressed?	Yes

Bibliographic reference	Schauwvlieghe A M. E; Dijkman G ; Hooymans J M; Verbraak F D; Hoyng C B; Dijkgraaf M G. W; Peto T ; Vingerling J R; Schlingemann R O. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. PLoS ONE 11 (5) 2016
Are reports of the study free of suggestion of selective outcome reporting?	Yes

Bibliographic reference	**Subramanian 2010** Subramanian ML, Abedi G, Ness S, Ahmed E, Fenberg M, Daly MK, et al. Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial. Eye 2010;24(11):1708-15.
Methods	**Number randomized (total and per group**): 28 participants randomly assigned to study treatment; 20 in bevacizumab group and 8 in ranibizumab group **Exclusions after randomization**: none **Number analyzed (total and per group):** 22 total participants; 15 in bevacizumab group and 7 in ranibizumab group **Unit of analysis:** individuals (one study eye per participant) **Losses to follow up**: six participants: three participants voluntarily dropped out (two in bevacizumab group, one in ranibizumab group); one participant relocated (in bevacizumab group); and two participants died (both in bevacizumab group) **Compliance**: 22/28 participants completed the study **Intention to treat analysis:** no, six participants enrolled and randomized were not included in analysis **Reported power calculation:** yes, 79% power for sample size of 135 participants using 2:1 randomization ratio **Study design comment:** although the target sample size was 135, only 28 participants were evaluated
Participants	**Country:** Boston, MA, USA **Age:** not reported for 28 enrolled participants (mean 78 years for analyzed bevacizumab group; mean 80 years for analyzed ranibizumab group) **Gender (percent):** not reported for 28 enrolled participants (all men for analyzed bevacizumab group; 6 men and 1 woman for analyzed ranibizumab group)

<table>
<tr><td></td><td>Inclusion criteria: age 50 years or older; presence of symptomatic CNV, confirmed by intravenous fluorescein angiogram and optical coherence tomography as affecting the foveal centre; ability to provide informed consent; willing to commit to regular clinic appointments and follow-up; original protocol specified baseline VA between 20/40 and 20/200, later amended to include all baseline VAs equal to or better than 20/400
Exclusion criteria: previous treatment for wet AMD within the past year; presence of subretinal hemorrhage greater than 50% of the size of the lesion on fluorescein angiography, presence of advanced glaucoma; any coexisting macular disease causing decreased vision; history of malignant or uncontrolled hypertension; intraocular inflammation; history of thromboembolic phenomena; inability to provide informed consent; participation in another concurrent ophthalmic clinical trial
Equivalence of baseline characteristics: yes
Diagnoses in participants: AMD</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 0.05 ml intravitreal bevacizumab injection (concentration not reported) every month for first three months; re-treatment afterwards based on OCT or VA changes
Intervention 2: 0.05 ml intravitreal ranibizumab injection (concentration not reported) every month for first three months; re-treatment afterwards based on OCT or VA changes
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>-</td><td>-</td></tr>
<tr><td>Frequency</td><td>Monthly for 3 months; retreatment based on OCT or VA changes</td><td>Monthly for 3 months, retreatment based on OCT or VA changes</td></tr>
</table>
Length of follow up: Planned: 12 months; Actual: 12 months</td></tr>
<tr><td>Outcomes</td><td>Primary outcomes, as defined: visual acuity
Secondary outcomes, as reported: central foveal thickness by OCT, total number of injections; blood pressure measurements
Adverse events
Intervals at which outcome assessed: one week after injections to assess adverse events; and monthly through 12 months</td></tr>
</table>

Results

Visual acuity (12 months)

	Bevacizumab (n=15)	Ranibizumab (n=7)	RR (95%CI)
Gain of ≥15 letters, n	5	1	2.33 (0.33, 16.41)
Loss of ≥15 letters	0	1	0.17 (0.01, 3.65)
Gain or loss less than 15 letters	10	5	0.93 (0.52, 1.68)

Number of injections (12 months)

	Bevacizumab (n=15)	Ranibizumab (n=7)
Median (range)	7 (3,8)	4 (3,6)

Notes

Type of study: published
Funding sources: Veterans Affairs Boston Healthcare System, USA
Declarations of interest: "The authors declare no conflict of interest"
Study period: April 2007 to February 2009
Reported subgroup analyses: none
Contacting study investigators: trial authors contacted and contributed information for this review

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were enrolled by a 2:1 randomization to either the bevacizumab (2) or the ranibizumab (1) arm of the study." Study investigators were contacted, but could not provide additional information as to how the sequence was generated (email communication with Dr Subramanian, dated 16 May 2012).
Allocation concealment (selection bias)	Low risk	"The Research Pharmacist at the [Veterans Affairs] Hospital Pharmacy was responsible for randomization" and "all subjects were assigned a study number."
Masking of participants (performance bias)	Low risk	Reported as "double-blind"; identical syringes were used to administer agents, and study personnel in contact with participants were all masked.
Masking of study personnel (performance bias)	Low risk	"To obtain blinding of treatment assignments, the Research Pharmacist at the [Veterans Affairs] Hospital Pharmacy was responsible for randomization, tracking and ensuring the correct study

		drug was administered to each patient at each visit, and dispensing the same volume of each drug in identical 1 ml syringes."
Masking of outcome assessment (detection bias)	Low risk	"To obtain blinding of treatment assignments, the Research Pharmacist at the [Veterans Affairs] Hospital Pharmacy was responsible for randomization, tracking and ensuring the correct study drug was administered to each patient at each visit, and dispensing the same volume of each drug in identical 1 ml syringes."
Incomplete outcome data (attrition bias)	Unclear risk	Six of 28 (21%) participants enrolled were not included in the analysis: three voluntarily dropped out; one relocated; and two died.
Selective reporting (reporting bias)	Low risk	Primary outcomes were reported; however, the clinical trials register record for this trial but not the published reports specified quality of life as an outcome.
Other bias	Low risk	None observed

Aflibercept vs ranibizumab

Bibliographic reference	**VIEW 1** Heier JS, Brown DM, Chong V, Korobelnik J-F, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 2012;119(12):2537-48.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomly assigned**: 1217 total participants (1217 eyes) • 304 in the aflibercept 0.5 mg every 4 weeks group • 304 in the aflibercept 2.0 mg every 4 weeks group • 303 in the aflibercept 2.0 mg every 8 weeks group • 306 in the ranibizumab group **Exclusions after randomization**: Full analysis: 7 total participants • 3 in the aflibercept 0.5 mg every 4 weeks group, 0 in the aflibercept 2.0 mg every 4 weeks group, 2 in the aflibercept 2.0 mg every 8 weeks group, and 2 in the ranibizumab group Safety analysis: 2 total participants (both in the ranibizumab group) **Losses to follow-up:** 103 participants discontinued treatment at 1-year follow-up

	• 30 in the aflibercept 0.5 mg every 4 weeks group • 16 in the aflibercept 2.0 mg every 4 weeks group • 30 in the aflibercept 2.0 mg every 8 weeks group • 27 in the ranibizumab group **Number analysed:** Full analysis - 1210 total participants at 1-year follow-up 301 in the aflibercept 0.5 mg every 4 weeks group 304 in the aflibercept 2.0 mg every 4 weeks group, 301 in the aflibercept 2.0 mg every 8 weeks group 304 in the ranibizumab group Safety analysis - 1215 total participants at 1-year follow-up 304 in the aflibercept 0.5 mg every 4 weeks group 304 in the aflibercept 2.0 mg every 4 weeks group 303 in the aflibercept 2.0 mg every 8 weeks group 304 in the ranibizumab group **Unit of analysis:** individual (1 study eye per participant) **How were missing data handled?** missing values imputed using last observation carried forward approach **Power calculation:** none reported
Participants	**Country**: United States and Canada (154 study sites) **Mean age** (range not reported): 78 years in the aflibercept 0.5 mg every 4 weeks group, 78 years in the aflibercept 2.0 mg every 4 weeks group, 78 years in the aflibercept 2.0 mg every 8 weeks group, and 78 years in the ranibizumab group **Gender**: 134 men (44.5%) and 167 women (55.5%) in the aflibercept 0.5 mg every 4 weeks group, 110 men (36.2%) and 194 women (63.8%) in the aflibercept 2.0 mg every 4 weeks group, 123 men (40.9%) and 178 women (59.1%) in the aflibercept 2.0 mg every 8 weeks group, and 132 men (43.4%) and 172 women (56.6%) in the ranibizumab group **Inclusion criteria:** 50 years of age or older; diagnosed with neovascular AMD in the study eye; active subfoveal CNV lesions of any subtype (12 optic disc areas or smaller) constituting ≥ 50% of total lesion size; BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters (20/40 to 20/320 Snellen equivalent); willingness and ability to return for clinic visits and complete study-related procedures; ability to provide informed consent

<table>
<tr><td></td><td>Exclusion criteria: prior or concomitant treatment for AMD in the study eye; prior treatment with anti-VEGF therapy; subretinal hemorrhage or scar or fibrosis constituting > 50% of total lesion size or involving the center of the fovea in the study eye; retinal pigment epithelial tears or rips involving the macula in the study eye; history of other ocular conditions such as vitreous hemorrhage, retinal detachment, macular hole, corneal transplant, corneal dystrophy, diabetic retinopathy, diabetic macular edema, uveitis, scleromalacia; presence of other ocular conditions such as uncontrolled glaucoma, significant media opacities, phakia or pseudophakia with absence of posterior capsule, intraocular inflammation or infection; prior vitrectomy, trabeculectomy, or other filtration surgery or therapy in the study eye
Equivalence of baseline characteristics: yes; "Baseline demographics and disease characteristics were evenly balanced among all treatment groups"</td></tr>
<tr><td>Interventions</td><td>Intervention 1: intravitreal aflibercept 0.5 mg every 4 weeks
Intervention 2: intravitreal aflibercept 2.0 mg every 4 weeks
Intervention 3: intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial doses at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8)
Intervention 4: intravitreal ranibizumab 0.5 mg every 4 weeks

<table>
<tr><th></th><th>Intervention1</th><th>Intervention2</th><th>Intervention3</th><th>Intervention4</th></tr>
<tr><td>Agent</td><td>aflibercept</td><td>aflibercept</td><td>aflibercept</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>Every 4 weeks</td><td>Every 8 weeks after 3 initial doses, sham injections were given at the interim 4-week visits after week8</td><td>Every 4 weeks</td></tr>
</table>

Length of follow-up: 1 year for primary end point; dosing for all groups changed to as needed (PRN) after 1 year and follow-up at 2 years from baseline</td></tr>
</table>

<table>
<tr><td>Outcomes</td><td>Primary outcome, as defined in study reports: "proportion of patients maintaining vision at week 52 (losing < 15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart)"
Secondary outcomes, as defined in study reports: change in BCVA, proportion gaining ≥ 15 letters, change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25) score, change in CNV area on fluorescein angiography, retinal thickness and persistent fluid as assessed by OCT, mean number of intravitreal injections, adverse events
Intervals at which outcomes assessed: every 4 weeks through 96 weeks; week 1 after first treatment for safety assessment; weeks 12, 24, 36, and 52 for the NEI-VFQ-25 assessment</td></tr>
<tr><td>Results</td><td>Visual acuity (52 weeks)
<table>
<tr><th></th><th>Aflibercept 0.5mg monthly (n=301)</th><th>Aflibercept 2.0mg monthly (n=304)</th><th>Aflibercept 2.0mg bi-monthly (n=301)</th><th>Ranibizumab 0.5mg monthly (n=304)</th></tr>
<tr><td>Loss of <15 letters, n(%)</td><td>286(95)</td><td>289 (95.1)</td><td>284 (94.4)</td><td>285 (93.8)</td></tr>
<tr><td>Gain of ≥15 letters</td><td>75 (24.9)</td><td>114 (37.5)</td><td>92 (30.6)</td><td>94 (30.9)</td></tr>
<tr><td>Loss of ≥15 letters</td><td>15</td><td>15</td><td>17</td><td>19</td></tr>
</table>
Adverse event (52 weeks)
<table>
<tr><th></th><th>Aflibercept 0.5mg monthly (n=304)</th><th>Aflibercept 2.0mg monthly (n=304)</th><th>Aflibercept 2.0mg bi-monthly (n=303)</th><th>Ranibizumab 0.5mg monthly (n=304)</th></tr>
<tr><td>Endophthalmitis</td><td>0</td><td>3</td><td>0</td><td>3</td></tr>
<tr><td>VA reduced</td><td>2</td><td>1</td><td>0</td><td>2</td></tr>
<tr><td>Retinal hemogghage</td><td>0</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>≥ 1 ocular SAE</td><td>6</td><td>7</td><td>3</td><td>10</td></tr>
</table></td></tr>
</table>

	Nonfatal myocardial infarction	4	1	1	4
	Nonfatal stroke	2	1	1	0
Notes	**Type of study reports**: published journal articles; clinical trial registration **Funding sources:** "Sponsored by Regeneron Pharmaceuticals, Inc, Tarrytown, New York, and Bayer HealthCare, Berlin Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript" **Disclosures of interest:** "J.S.H. is a consultant to and has received research funding from Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, and Regeneron Pharmaceuticals. He has also received travel support from Regeneron Pharmaceuticals. D.M.B. is a consultant to Alimera, Allergan, Bayer, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, and Thrombogenics and has received research funding from Alcon, Alimera, Allergan, Eli Lilly, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, and Thrombogenics. He has also received travel support from Regeneron Pharmaceuticals and lecture fees from Genentech. V.C. is a consultant to Alimera and Bayer and has received research funding from Alcon, Allergan, Bayer, Novartis, and Pfizer. He is an advisory board member for Allergan and Novartis and has also received travel support from Bayer. J.-F.K. is a consultant to Alcon, Bayer, and Thea and an advisory board member for Allergan, Bayer, and Novartis. He has received travel support from Regeneron Pharmaceuticals. P.K.K. is a consultant to Bayer, Genentech, Novartis, and Regeneron Pharmaceuticals. He has received research funding from Regeneron Pharmaceuticals. Q.D.N. is a consultant to Bausch & Lomb and Santen and has received research funding from Genentech, Novartis, and Pfizer. B.K. has received travel support from Bayer. A.H. is a consultant to Alcon, Allergan, Centocor, Johnson & Johnson, Neovista, Merck, Ophthotech, Oraya, Paloma, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Thrombogenics. He has received research funding and lecture fees from Alcon, Allergan, Genentech, Neovista, Ophthotech, Oraya, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Second Sight. Y.O. is a consultant to Alcon and Bayer and has received travel support from Bayer. G.D.Y., N.S., R.V., A.J.B., and Y.S. are employees of Regeneron Pharmaceuticals. M.A., G.G., B.S., and R.S. are employees of Bayer HealthCare. C.S.'s institution has received payments from the Medical University of Vienna for data monitoring/reviewing and statistical analysis. U.S.-E. is a consultant to Alcon, Allergan, Bayer HealthCare, and Novartis, and an advisory board member for Alcon and Novartis. She has received travel support from Bayer HealthCare and lecture fees from Bayer HealthCare and Novartis" **Study period**: July 2007 to September 2010				

	Subgroup analyses: none reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was unclear. “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Allocation concealment (selection bias)	Low risk	Central randomization: “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Masking of participants and personnel (performance bias)	Low risk	“Patients were masked as to treatments. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose...All other study site personnel were masked to treatment assignment by separating study records or masked packaging”
Masking of outcome assessment (detection bias)	Low risk	“A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment”
Incomplete outcome data (attrition bias)	Low risk	A full analysis set and a per protocol set were reported. Last observation carried forward (LOCF) approach was used to impute missing values; 91.1% to 96.4% of participants per treatment group completed 52 weeks of follow-up
Selective reporting (reporting bias)	Low risk	The study was registered at clinicaltrials.gov; intended outcomes were reported
Other bias	High risk	Many authors are employees of, consultants to, or have received research funding from Regeneron Pharmaceuticals, which manufactures aflibercept and participated in the design of the trial, collected and analyzed data, and prepared the study reports

Bibliographic reference	VIEW 2

	Heier JS, Brown DM, Chong V, Korobelnik J-F, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 2012;119(12):2537-48.
Methods	**Study design:** parallel-group randomized controlled trial **Number randomly assigned**: 1240 total participants (1240 eyes) 311 in the aflibercept 0.5 mg every 4 weeks group 313 in the aflibercept 2.0 mg every 4 weeks group 313 in the aflibercept 2.0 mg every 8 weeks group 303 in the ranibizumab group **Exclusions after randomization:** Full analysis - 38 total participants: 15 in the aflibercept 0.5 mg every 4 weeks group 4 in the aflibercept 2.0 mg every 4 weeks group 7 in the aflibercept 2.0 mg every 8 weeks group 12 in the ranibizumab group Safety analysis - 36 total participants: 14 in the aflibercept 0.5 mg every 4 weeks group 4 in the aflibercept 2.0 mg every 4 weeks group 6 in the aflibercept 2.0 mg every 8 weeks group 12 in the ranibizumab group **Losses to follow-up:** 148 participants discontinued treatment at 1-year follow-up 45 in the aflibercept 0.5 mg every 4 weeks group 37 in the aflibercept 2.0 mg every 4 weeks group 33 in the aflibercept 2.0 mg every 8 weeks group 33 in the ranibizumab group **Number analyzed:** Full analysis - 1202 total participants at 1-year follow-up 296 in the aflibercept 0.5 mg every 4 weeks group 309 in the aflibercept 2.0 mg every 4 weeks group 306 in the aflibercept 2.0 mg every 8 weeks group 291 in the ranibizumab group

	Safety analysis - 1204 total participants at 1-year follow-up 297 in the aflibercept 0.5 mg every 4 weeks group 309 in the aflibercept 2.0 mg every 4 weeks group 307 in the aflibercept 2.0 mg every 8 weeks group 291 in the ranibizumab group **Unit of analysis:** individual (1 study eye per participant) **How were missing data handled**? missing values imputed using last observation carried forward approach **Power calculation**: none reported
Participants	**Country:** Argentina; Australia; Austria; Brazil; Belgium; Colombia; Czech Republic; France; Germany; Hungary; India; Israel; Italy; Japan; Latvia; Mexico; Netherlands; Poland; Portugal; South Korea; Singapore; Slovakia; Spain; Sweden; Switzerland; United Kingdom (172 study sites) **Mean age** (range not reported): 75 years in the aflibercept 0.5 mg every 4 weeks group, 74 years in the aflibercept 2.0 mg every 4 weeks group, 74 years in the aflibercept 2.0 mg every 8 weeks group, and 73 years in the ranibizumab group **Gender:** 149 men (50.3%) and 147 women (49.7%) in the aflibercept 0.5 mg every 4 weeks group, 133 men (43.0%) and 176 women (57.0%) in the aflibercept 2.0 mg every 4 weeks group, 131 men (42.8%) and 175 women (57.2%) in the aflibercept 2.0 mg every 8 weeks group, and 122 men (41.9%) and 169 women (58.1%) in the ranibizumab group **Inclusion criteria:** 50 years or older; diagnosed with neovascular AMD in the study eye; active subfoveal CNV lesions of any subtype (12 optic disc areas or fewer) constituting ≥ 50% of total lesion size; BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters (20/40 to 20/320 Snellen equivalent); willingness and ability to return for clinic visits and complete study-related procedures; ability to provide informed consent **Exclusion criteria**: prior or concomitant treatment for AMD in the study eye; prior treatment with anti-VEGF therapy; subretinal hemorrhage or scar or fibrosis constituting > 50% of total lesion size or involving the center of the fovea in the study eye; retinal pigment epithelial tears or rips involving the macula in the study eye; history of other ocular conditions such as vitreous hemorrhage, retinal detachment, macular hole, corneal transplant, corneal dystrophy, diabetic retinopathy, diabetic macular edema, uveitis, scleromalacia; presence of other ocular conditions such as uncontrolled glaucoma, significant media opacities, phakia or pseudophakia with absence of posterior capsule, intraocular inflammation or infection; prior vitrectomy, trabeculectomy, or other filtration surgery or therapy in the study eye **Equivalence of baseline characteristics**: yes; "Baseline demographics and disease characteristics were evenly balanced among all treatment groups"

<table>
<tr><td>Interventions</td><td>
Intervention 1: intravitreal aflibercept 0.5 mg every 4 weeks
Intervention 2: intravitreal aflibercept 2.0 mg every 4 weeks
Intervention 3: intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial doses at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8)
Intervention 4: intravitreal ranibizumab 0.5 mg every 4 weeks
<table>
<tr><td></td><td>Intervention1</td><td>Intervention2</td><td>Intervention3</td><td>Intervention4</td></tr>
<tr><td>Agent</td><td>aflibercept</td><td>aflibercept</td><td>aflibercept</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>Every 4 weeks</td><td>Every 8 weeks after 3 initial doses, sham injections were given at the interim 4-weeks visits after week8</td><td>Every 4 weeks</td></tr>
</table>
Length of follow-up: 1 year for primary end point; dosing for all groups changed to as needed (PRN) after 1 year and follow-up at 2 years from baseline
</td></tr>
<tr><td>Outcomes</td><td>
Primary outcome, as defined in study reports: "proportion of patients maintaining vision at week 52 (losing < 15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart)"
Secondary outcomes, as defined in study reports: change in BCVA and anatomic measures, proportion gaining ≥ 15 letters, change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25) score, change in CNV area on fluorescein angiography, retinal thickness and persistent fluid as assessed by OCT, mean number of intravitreal injections, adverse events
Intervals at which outcomes assessed: every 4 weeks through 96 weeks; week 1 after first treatment for safety assessment; weeks 12, 24, 36, and 52 for the NEI-VFQ-25 assessment
</td></tr>
</table>

Results

Visual acuity (52 weeks)

	Aflibercept 0.5mg monthly (n=296)	Aflibercept 2.0mg monthly (n=309)	Aflibercept 2.0mg bi-monthly (n=306)	Ranibizumab 0.5mg monthly (n=291)
Loss of <15 letters, n(%)	282 (95.3)	292 (94.5)	292 (94.5)	276 (94.8)
Gain of ≥15 letters	103 (34.8)	91 (29.4)	96 (31.4)	99 (34.0)
Loss of ≥15 letters	14	17	14	15

Adverse event (52 weeks)

	Aflibercept 0.5mg monthly (n=297)	Aflibercept 2.0mg monthly (n=309)	Aflibercept 2.0mg bi-monthly (n=307)	Ranibizumab 0.5mg monthly (n=291)
Endophthalmitis	0	0	0	0
VA reduced	1	1	5	1
Retinal hemogghage	1	1	2	1
≥ 1 ocular SAE	5	6	9	9
Nonfatal myocardial infarction	2	2	5	2
Nonfatal stroke	1	1	2	2

Notes

Type of study reports: published journal articles; clinical trial registration
Funding sources: "Sponsored by Regeneron Pharmaceuticals, Inc, Tarrytown, New York, and Bayer HealthCare, Berlin Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript"

	Disclosures of interest: "J.S.H. is a consultant to and has received research funding from Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, and Regeneron Pharmaceuticals. He has also received travel support from Regeneron Pharmaceuticals. D.M.B. is a consultant to Alimera, Allergan, Bayer, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, and Thrombogenics and has received research funding from Alcon, Alimera, Allergan, Eli Lilly, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, and Thrombogenics. He has also received travel support from Regeneron Pharmaceuticals and lecture fees from Genentech. V.C. is a consultant to Alimera and Bayer and has received research funding from Alcon, Allergan, Bayer, Novartis, and Pfizer. He is an advisory board member for Allergan and Novartis and has also received travel support from Bayer. J.-F.K. is a consultant to Alcon, Bayer, and Thea and an advisory board member for Allergan, Bayer, and Novartis. He has received travel support from Regeneron Pharmaceuticals. P.K.K. is a consultant to Bayer, Genentech, Novartis, and Regeneron Pharmaceuticals. He has received research funding from Regeneron Pharmaceuticals. Q.D.N. is a consultant to Bausch & Lomb and Santen and has received research funding from Genentech, Novartis, and Pfizer. B.K. has received travel support from Bayer. A.H. is a consultant to Alcon, Allergan, Centocor, Johnson & Johnson, Neovista, Merck, Ophthotech, Oraya, Paloma, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Thrombogenics. He has received research funding and lecture fees from Alcon, Allergan, Genentech, Neovista, Ophthotech, Oraya, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Second Sight. Y.O. is a consultant to Alcon and Bayer and has received travel support from Bayer. G.D.Y., N.S., R.V., A.J.B., and Y.S. are employees of Regeneron Pharmaceuticals. M.A., G.G., B.S., and R.S. are employees of Bayer HealthCare. C.S.'s institution has received payments from the Medical University of Vienna for data monitoring/reviewing and statistical analysis. U.S.-E. is a consultant to Alcon, Allergan, Bayer HealthCare, and Novartis, and an advisory board member for Alcon and Novartis. She has received travel support from Bayer HealthCare and lecture fees from Bayer HealthCare and Novartis" **Study period**: March 2008 to September 2010 **Subgroup analyses**: yes; Japanese subgroup

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was unclear. "Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system"

Allocation concealment (selection bias)	Low risk	Central randomization: “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Masking of participants and personnel (performance bias)	Low risk	“Patients were masked as to treatments. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose...All other study site personnel were masked to treatment assignment by separating study records or masked packaging”
Masking of outcome assessment (detection bias)	Low risk	“A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment”
Incomplete outcome data (attrition bias)	Low risk	A full analysis set and a per protocol set were reported. Last observation carried forward (LOCF) approach was used to impute missing values; 88.1% to 91.1% of participants per treatment group completed 52 weeks of follow-up
Selective reporting (reporting bias)	Low risk	Study was registered at clinicaltrials.gov; intended outcomes were reported
Other bias	High risk	Many authors are employees of, consultants to, or have received research funding from Regeneron Pharmaceuticals, which manufactures aflibercept and participated in the design of the trial, collected and analyzed data, and prepared the study reports

The Yuzawa study described below was identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

Bibliographic reference	**Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015**
Country/ies	VIEW1 (154 sites in the USA and Canada); VIEW 2 (172 sites in Europe, the Middle East, Asia-Pacific region and Latin America)
Study type	RCT
Aim of the study	To evaluate the effect of intravitreal aflibercept injection on visual function in wet age-related macular degeneration (AMD)
Study dates	Published 2015

Bibliographic reference	**Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015**
Sources of funding	Medical writing support was funded by Bayer Parma AG
Sample size	2419
Inclusion Criteria	50 years of age or older; diagnosed with neovascular AMD in the study eye; active subfoveal CNV lesions of any subtype (12 optic disc areas or smaller) constituting ≥ 50% of total lesion size; BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters (20/40 to 20/320 Snellen equivalent); willingness and ability to return for clinic visits and complete study-related procedures; ability to provide informed consent
Exclusion Criteria	Prior or concomitant treatment for AMD in the study eye; prior treatment with anti-VEGF therapy; subretinal hemorrhage or scar or fibrosis constituting > 50% of total lesion size or involving the center of the fovea in the study eye; retinal pigment epithelial tears or rips involving the macula in the study eye; history of other ocular conditions such as vitreous hemorrhage, retinal detachment, macular hole, corneal transplant, corneal dystrophy, diabetic retinopathy, diabetic macular edema, uveitis, scleromalacia; presence of other ocular conditions such as uncontrolled glaucoma, significant media opacities, phakia or pseudophakia with absence of posterior capsule, intraocular inflammation or infection; prior vitrectomy, trabeculectomy, or other filtration surgery or therapy in the study eye
Baseline characteristics	

	VIEW 1		VIEW2	
	Aflibercept (2mg, q8)	Ranibizumab (0.5mg,q4)	Aflibercept (2mg, q8)	Ranibizumab (2mg, q4)
No.	301	304	306	291
Mean age (SD)	77.9 (8.4)	78.2 (7.6)	73.8 (8.6)	73.0 (9.0)
Male: n (%)	123 (40.9)	132 (43.4)	131 (42.8)	12 (41.9)
Race, White: n(%)	287 (95.3)	296 (97.4)	217 (70.9)	213 (73.2)
Mean BCVA in study eye (SD)	55.7 (12.8)	54.0 (13.4)	51.6 (13.9)	53.8 (13.5)
NEI-VFQ25 score				
No. reported	293	303	306	291
Composite score	69.6 (16.8)	71.8 (17.2)	71.3 (19.1)	72.9 (19.1)
Subscale score				

Bibliographic reference	Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015

General vision	59.4 (17.2)	60.0 (17.4)	56.1 (16.5)	57.0 (17.0)
Near activies	61.2 (21.4)	62.8 (22.6)	60.9 (26.4)	63.7 (25.5)
Distance activies	65.3 (22.3)	69.1 (22.7)	70.6 (25.7)	70.8 (27.1)
Metal health	57.5 (25.6)	62.0 (25.4)	60.5 (27.6)	62.6 (26.5)
Social functioning	82.6 (21.8)	85.0 (19.5)	83.1 (22.8)	85.4 (22.1)
Dependency	73.3 (24.9)	75.3 (27.0)	76.7 (28.8)	80.0 (28.8)
Role difficulities	64.8 (25.0)	66.3 (27.8)	60.3 (31.5)	64.1 (31.2)
Driving	55.8 (30.3)	58.0 (30.5)	55.4 (36.3)	57.7 (35.3)
Colour vision	85.1 (22.2)	88.7 (19.0)	89.7 (20.2)	90.1 (19.8)
Peripheral vision	76.1 (23.5)	77.3 (23.3)	79.1 (25.8)	81.0 (24.2)
Ocular pain	82.4 (18.1)	84.5 (18.2)	84.0 (20.0)	82.4 (21.0)
General health	65.2 (22.5)	64.2 (21.6)	49.5 (21.2)	50.2 (21.1)

Study visits and procedures	Patients were randomized in a 1:1:1:1ratio to1of3 intravitreal aflibercept dosing regimens(0.5q4 or 2.0mgevery4weeks;2.0mg every 8weeks[2q8]) or t oranibizumab 0.5q4; All treatment groups received injections of the assigned drug at weeks 0,4,and 8(sham injections were given to the intravitreal aflibercept 2q8 group at each interim visit after the initial 3 injections to maintain masking). The study eye in those with bilateral wet AMD was the worse-seeing eye. If VA was similar in both eyes, additional criteria were specified to determine the study eye.The fellow eye could be treated outside of the study according to the prevailing standard of care.
Intervention	Intravitreal aflibercept 2.0mg every 4 weeks, 2.0mg every 8 weeks, or 0.5mg every 4 weeks.
Comparator	Intravitreal ranibizumab 0.5mg every 4 weeks.
Outcomes	The NEIVFQ-25 assessments were conducted by trained interviewers who were masked to treatment arm assignment.The NEI VFQ-25 was administered at the following time points: screening (visit1) and weeks 12, 24, 36 and 52. InVIEW1, the instrument was administered by telephone; inVIEW2, it was administered face to face.The NEIVFQ-25 scores were calculated according to standard scoring protocols published by the instrument's developers.28 In both studies, mean

<table>
<tr><th>Bibliographic reference</th><th>Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015</th></tr>
<tr><td></td><td>change from baseline to week52 in composite score was a secondary efficacy outcome and mean change from baseline to week 52 in subscale scores was an exploratoryefficacy outcome measure.</td></tr>
<tr><td>Analyses</td><td>All planned analyses were performed in the full analysis set population (subjects who received any study medication and had at least 1 post baseline assessment) separately for each study (protocol specified). One additional analysis was performed in the pooled data set that compared mean change from baseline with week 52 in composite and subscale scores, in subgroups of patients, based on the status of the heterolateral eye.
Missing data were imputed using last observation carried forward; descriptive statistics reported here are mean and standard deviation. Sensitivity analyse susing observed cases were performed to assess the robustness of the analysis.</td></tr>
<tr><td>Length of follow up</td><td>52 weeks</td></tr>
<tr><td>Result</td><td>Mean change NEI-VFQ from baseline to week 52

Mean change in NEI-VFQ25 composite socre by clinical reponse
VIEW 1
<table>
<tr><td></td><td colspan="3">Mean change in composite score, no.</td></tr>
<tr><td></td><td>Aflibercept, 2.0mg, q8 (no. of people) (total=293)</td><td>Raibizumab 0.5mg, q4 (no. of people) (total=304)</td><td>Effect, RR (95%CI)</td></tr>
<tr><td>Loss of >5 EDTRS letters</td><td>-2.3 (34 people)</td><td>-2.5 (32 people)</td><td>1.10 (0.70, 1.73)</td></tr>
<tr><td>Change of ≥5 and ≤ 5 EDTRS letters</td><td>1.5 (73 people)</td><td>3.8 (63 people)</td><td>2.10 (0.89, 1.61)</td></tr>
<tr><td>Gain of >5 EDTRS letters</td><td>7.2 (192 people)</td><td>8.5 (192 people)</td><td>1.03 (0.92, 1.17)</td></tr>
</table>
VIEW 2</td></tr>
</table>

Bibliographic reference	Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015

	Mean change in composite score, no.		
	Aflibercept, 2.0mg, q8 (no. of people) (total=306)	Raibizumab 0.5mg, q4 (no. of people) (total=291)	Effect, RR (95%CI)
Loss of >5 EDTRS letters	-1.9 (38 people)	-0.1 (40 people)	0.90 (0.60, 1.37)
Change of ≥5 and ≤ 5 EDTRS letters	4.8 (72 people)	2.0 (70 people)	0.98 (0.73, 1.30)
Gain of >5 EDTRS letters	7.1 (182 people)	7.0 (190people)	0.90 (0.80, 1.03)

Mean change in NEI-VFQ25 subscale score
VIEW1

	Aflibercept (2.0mg, q8)	Ranibizumab (0.5mg, q4)	Effect, MD (95%CI)
No. (at basline)	293	303	
General vision	10.1 (19.0)	9.5 (18.8)	0.60 (-2.44, 3.64)
Near activies	6.1 (19.0)	7.2 (23.1)	-1.10 (-4.74, 2.54)
Distance activies	6.2 (21.8)	2.5 (23.1)	3.70 (0.10, 7.30)
Metal health	10.1 (24.1)	9.8 (21.8)	0.30 (-3.39, 3.99)
Social functioning	2.6 (22.1)	3.0 (20.0)	-0.40 (-3.85, 3.05)
Dependency	3.4 (22.9)	5.4 (22.6)	-2.00 (-5.65, 1.65)
Role difficulities	7.1 (26.7)	5.8 (29.3)	1.30 (-3.20, 5.80)

Bibliographic reference	Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015

Driving	2.2 (24.4)	0.1 (22.0)	2.10 (-1.63, 5.83)
Colour vision	0.6 (22.3)	1.9 (19.1)	-1.30 (-4.64, 2.04)
Peripheral vision	4.4 (23.9)	5.5 (25.3)	-1.10 (-5.05, 2.85)
Ocular pain	1.2 (20.0)	1.3 (17.7)	-0.10 (-3.14, 2.94)
General health	-4.9 (22.1)	-3.6 (20.4)	-1.30 (-4.72, 2.12)

VIEW 2

	Aflibercept (2.0mg, q8)	Ranibizumab (0.5mg, q4)	Effect (95%CI)
No. (at basline)	306	291	
General vision	9.1 (17.0)	9.5 (18.1)	-0.40 (-3.22, 2.42)
Near activies	7.0 (21.3)	7.2 (21.1)	-0.20 (-3.60, 3.20)
Distance activies	4.3 (21.8)	7.6 (21.6)	-3.30 (-6.78, 0.18)
Metal health	10.4 (22.0)	11.2 (23.9)	-0.80 (-4.49, 2.89)
Social functioning	1.5(19.9)	4.9 (20.0)	-3.40 (-6.60, -0.20)
Dependency	4.1 (25.2)	4.5 (25.5)	-0.40 (-4.47, 3.67)
Role difficulities	7.8 (24.1)	6.9 (29.9)	0.90 (-3.47, 5.27)
Driving	1.0 (24.0)	0.1 (23.2)	0.90 (-2.89,4.69)
Colour vision	0.4 (21.2)	3.1(18.2)	-2.70 (-5.86, 0.46)
Peripheral vision	2.5 (25.7)	3.1 (26.2)	-0.60 (-4.77, 3.57)
Ocular pain	3.1 (19.4)	5.1 (22.7)	-2.00 (-5.40,1.40)
General health	1.5 (19.0)	0.8 (20.6)	0.70 (-2.48, 3.88)

Missing data handling/loss to follow up	Missing data were imputed using last observation carried forward; descriptive statistics reported here are mean and standard deviation. Sensitivity analyse susing observed cases were performed to assess the robustness of the analysis.

Bibliographic reference	Yuzawa M ; Fujita K ; Wittrup-Jensen Ku ; Norenberg C ; Zeitz O ; Adachi K ; Wang Ec ; Heier J ; Kaiser P ; Chong V ; Korobelnik Jf. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology 122 (3): 571-8, 2015
Was allocation adequately concealed?	Central randomization: “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Was knowledge of the allocated intervention adequately prevented during the study?	“Patients were masked as to treatments. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose...All other study site personnel were masked to treatment assignment by separating study records or masked packaging”
Was the allocation sequence adequately generated?	The method of random sequence generation was unclear. “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Was the study apparently free of other problems that could put it at a high risk of bias?	Yes
Were incomplete outcome data adequately addressed?	A full analysis set and a per protocol set were reported. Last observation carried forward (LOCF) approach was used to impute missing values; 88.1% to 91.1% of participants per treatment group completed 52 weeks of follow-up
Are reports of the study free of suggestion of selective outcome reporting?	Study was registered at clinicaltrials.gov; intended outcomes were reported

Effectiveness of treatment frequency of antiangiogenic therapies

Regular frequencies (routine injections)

Bibliographic reference	**Lushchyk 2013** Lushchyk T, Amarakoon S, Martinez-Ciriano JP, Born LI, Baarsma GS, Missotten T. Bevacizumab in age-related macular degeneration: A randomized controlled trial on the effect of injections every 4 weeks, 6 weeks and 8 weeks. Acta Ophthalmologica 2013;91(6):e456-61.
Methods	**Study design**: parallel-group randomized controlled trial

	Number randomized (total and per group): 191 total participants; 64 in the every 8 weeks group; 63 in the every 6 weeks group; 64 in the every 4 weeks group **Exclusions after randomization**: 2 participants due to lack of evidence of choroidal neovascularization **Number analyzed (total and per group):** 54 in the every 8 weeks group; 57 in the every 6 weeks group; 46 in the every 4 weeks group for efficacy analysis **Unit of analysis**: individual (one study eye per participant) **Losses to follow up**: 18 (28.1%) in the IVB every 4 weeks group; 6 (9.5%) in the IVB every 6 weeks group; 10 (15.6%) in the IVB every 8 weeks group **Intention to treat analysis:** no, participants with missing data excluded from analyses **Power calculation**: Yes; 80% **Study design comment**: single center trial
Participants	**Country**: Netherlands **Mean age:** 77 years **Gender (percent):** male 18(28.1%) and female 46(71.9%) in the IVB every 4 weeks group; male 25(39.7%) and female 38(60.3%) in the IVB every 6 weeks group; male 21(32.8%) and female 43(67.2%) in the IVB every 8 weeks group **Inclusion criteria**: 65 years of age or older; visual acuity of 20/200 to 20 /20 (Snellen equivalent) assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts; previously untreated active choroidal neovascularization due to ARMD; presence of active leakage to establish active choroidal neovascularization defined as a leakage observed using fluorescein angiography (FA) and indocyanine green (ICG) angiography, and the presence of fluid, observed using spectral-domain optical coherence tomography (OCT), located either below the retina or below the retinal pigment epithelium **Exclusion criteria:** other significant ocular disorders affecting visual; allergy to either FA or ICG dye injections was known; patients with immunocompromised or patients with an ocular surgery planned during the 1-year follow-up period; patients who used coumarin derivatives at the time of inclusion and patients who experienced clinically significant cerebrovascular accident or myocardial infarction in the 6 months prior to planned inclusion **Equivalence of baseline characteristics**: Yes

<table>
<tr><td>Interventions</td><td>Intervention 1: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05-ml solution) every 4 weeks
Intervention 2: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05-ml solution) every 6 weeks
Intervention 3: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05-ml solution) every 8 weeks
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention3</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td><td>1.25mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>Every 6 weeks</td><td>Every 8 weeks</td></tr>
</table>
Follow-up: 1 year
Frequency of assessments for retreatment: every 12 weeks in addition to regular injection visits</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: best-corrected visual acuity (BCVA)
Secondary outcomes, as defined: fluid and foveal thickness on spectral-domain OCT
Adverse events: Yes
Intervals at which outcome assessed: every 12 weeks</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)
<table>
<tr><th></th><th>Bevacizumab (n=46)</th><th>Bevacizumab (n=57)</th><th>Bevacizumab (n=54)</th></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td><td>1.25mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>Every 6 weeks</td><td>Every 8 weeks</td></tr>
<tr><td>Gain of ≥15 letters, n (%)</td><td>6 (13.0)</td><td>8 (14.1)</td><td>7 (13.0)</td></tr>
<tr><td>Loss of ≥15 letters</td><td>3 (6.5)</td><td>6 (10.5)</td><td>0 (0)</td></tr>
<tr><td>Gain or loss of less than 15 letters</td><td>37</td><td>43</td><td>47</td></tr>
</table>
Adverse event
<table>
<tr><th></th><th>Bevacizumab (n=64)</th><th>Bevacizumab (n=63)</th><th>Bevacizumab (n=64)</th></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td><td>1.25mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>Every 6 weeks</td><td>Every 8 weeks</td></tr>
<tr><td>Total SAEs, no</td><td>9</td><td>4</td><td>9</td></tr>
</table></td></tr>
</table>

	Atherothrombotic event	2	1	1
	Endophthalmitis	1	0	0
	Death from vascular cause	2	1	0
Notes	**Full study name**: not reported **Trial registration**: NTR117 **Funding sources:** not reported **Declarations of interest**: not reported **Study period:** June 2008 to March 2011 **Subgroup analyses:** none reported			

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Masking of participants and personnel (performance bias)	High risk	This study was “open-label” study.
Masking of outcome assessment (detection bias)	High risk	This study was “open-label” study.
Incomplete outcome data (attrition bias)	High risk	Although this paper claimed that intention-to-treat analysis was followed, 34 (17.8%) participants [18 (28.1%) in the IVB every 4 weeks group; 6 (9.5%) in the IVB every 6 weeks group; 10 (15.6%) in the IVB every 8 weeks group] were not included in the final efficacy analysis.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported in the final report.
Other bias	Unclear risk	Funding sources and declarations of interest were not reported.

Bibliographic reference	**NATTB 2013** Li X, Hu Y, Sun X, Zhang J, Zhang M, Neovascular Age-Related Macular Degeneration Treatment Trial Using Bevacizumab (NATTB). Bevacizumab for neovascular age-related macular degeneration in China. Ophthalmology 2012;119(10):2087-93.
Methods	**Study design**: cluster randomized controlled trial **Number randomized (total and per group):** 13 centers, 185 participants in total; 91 in the intervention 1; 94 in the intervention 2 **Exclusions after randomization:** none reported **Number analyzed (total and per group):** 79 eyes (86.8%) in the intervention 1; 82 eyes (87.2%) in the intervention 2 **Unit of analysis:** individual (one study eye per participant) **Losses to follow up**: not reported **Intention to treat analysis**: no **Power calculation**: none reported **Study design comment:** none reported
Participants	**Country:** China **Age(mean ± SD**): median 67 years in the intervention 1; median 70 years in the intervention 2 **Gender (percent):** male 60(65.9%) and female 31(34.4%) in the intervention 1; male 62(66.0%) and female 32(34.0%) in the intervention 2 **Inclusion criteria:** age of 50 years or more; previously untreated active choroidal neovascularization (determined by the presence of leakage, as seen on fluorescein angiography, and by the presence of fluid, as seen on OCT, located either within or under the neurosensory retina or under the retinal pigment epithelium) resulting from AMD; a lesion area of 12 disc areas or less, and best-corrected visual acuity between 5 and 73 letters using the Early Treatment Diabetic Retinopathy Study charts **Exclusion criteria**: presence of a macular scar, choroidal neovascularization not resulting from AMD, and polypoidal choroidal vasculopathy **Equivalence of baseline characteristics**: Yes
Interventions	Intervention 1: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05ml solution) every 6 weeks for 8 injections Intervention 2: intravitreal bevacizumab (1.25 mg bevacizumab in a 0.05ml solution) every 6 weeks for the first 3 injections, followed by injections every 12 weeks for the last 2 injections

	Intervention 1	**Intervention 2**
Agent	Bevacizumab	Bevacizumab
Dose	1.25mg	1.25mg
Frequency	Every 6 weeks for 8 injections	Every 6 weeks for first 3 injection, then every 12 weeks for 2 injections

Follow-up: 48 weeks
Frequency of assessments for retreatment: not reported

Outcomes	**Primary outcome,** as defined: mean change in visual acuity **Secondary outcomes,** as defined: proportion of patients with a change in visual acuity of 15 letters or more; the number of injections; the change in central retinal thickness on OCT,; the incidence of ocular and systemic adverse events; and annual drug cost **Adverse events**: Yes **Intervals at which outcome assessed**: every 6 weeks

Results

Visual acuity (12 months)

	Bevacizumab (n=79)	Bevacizumab (n=82)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	Every 6 weeks for 8 injections	Every 6 weeks for first 3 injection, then every 12 weeks for 2 injections	
Gain of ≥15 letters, no.	35	33	1.10 (0.77, 1.58)
Loss of ≥15 letters	3	5	0.62 (0.15, 2.52)
Gain or loss between 14 letters	41	44	0.97 (0.72, 1.30)

Adverse event after enrolment (12 months)

	Bevacizumab (n=91)	Bevacizumab (n=94)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	Every 6 weeks for 8 injections	Every 6 weeks for first 3 injection, then every 12 weeks for 2 injections	
Sterile inflammation, n(%)	17 (18.7)	9 (9.6)	1.95 (0.92, 4.15)
Headache	4 (4.4)	1 (1.1)	4.13 (0.47, 36.27)

Number of injections (48 weeks)

Agent	Bevacizumab (n=79)	Bevacizumab (n=82)
Dose	1.25mg	1.25mg
Frequency	Every 6 weeks for 8 injections	Every 6 weeks for first 3 injection, then every 12 weeks for 2 injections

	Mean number of injections (SD not reported)	7.86	4.89

Notes	**Full study name**: Bevacizumab for Neovascular Age-related Macular Degeneration in China **Trial registration:** NCT01306591 **Funding sources:** "Supported by the National Key Technology Research and Development Program in the 11th Five-Year Plan of China (no. 2006BAI02B05)." **Declarations of interest**: "The author(s) have no proprietary or commercial interest in any materials discussed in this article" **Study period:** January 2008 to January 2010 **Subgroup analyses**: none reported	
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported

Masking of participants (performance bias)	High risk	This study was “open-label” study
Masking of outcome assessment (detection bias)	Low risk	“Visual acuity examiners and imaging technicians were unaware of study group assignment” “A medical monitor who was unaware of study group assignments reviewed all adverse event data.”; masking of other outcome assessors was not reported
Incomplete outcome data (attrition bias)	High risk	24(13.0%) participants[12(13.2%) in the IVB every 6 weeks group; 12(12.8%) in the IVB every 6 weeks followed by every 12 weeks group] were not included in the final efficacy analysis
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported in the final report
Other bias	Low risk	none

Bibliographic reference	Schmidt-Erfurth Ursula, Eldem B, Guymer R, Korobelnik J F, Schlingermann R, Axer-Siegel R, Wiedemann P, Simader C, Gekkieva M, Weichsellberge A. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration. The American Academy of Ophthalmology 2010. (EXCITE)
Methods	**Study design**: randomised, double-masked, active-controlled multicentre study **Number randomized (total and per group):** 353 patients randomised for treatment including 120 patients in 0.3mg quarterly treatment arm; 118 patients in 0.5mg quarterly treatment arm; and 115 patients in 0.3mg monthly treatment arm. **Exclusions after randomization**: none **Number analyzed (total and per group):** 120 patients in 0.3mg quarterly treatment arm; 118 patients in 0.5mg quarterly treatment arm; and 115 patients in 0.3mg monthly treatment arm for efficacy analysis **Unit of analysis**: individual (one study eye per participant) **Losses to follow up**: 14 (11.7%) in 0.3mg quarterly treatment arm; 23(19.5%) in 0.5mg quarterly treatment arm; 12 (10.4%) in 0.3mg monthly treatment arm **Intention to treat analysis:** Yes **Power calculation**: Yes; 87% **Study design comment**: multi-center trial

<table>
<tr><td>Participants</td><td>Country: 16 European countries.
Mean age: 75.3 (SD=7.56) years
Gender (percent): male 50(41.7%) and female 70(58.3%) in the 0.3mg quarterly treatment arm; male 45(38.1%) and female 73(61.9%) in 0.5mg quarterly treatment arm; male 49(42.6%) and female 66(57.4%) in the 0.3mg monthly treatment arm
Inclusion criteria: ≥50 years of age or older; primary or recurrent subfoveal CNV secondary to AMD, with predominantly, classic, minimally classic, or occult (with no classic component) lesions. BCVA score between 73 and 24 letters (appropriately 20/40 to 20/320 Snellen equivalent).
Exclusion criteria: BCVA score of <34 letters in both eyes; previous treatment or participation in a clinical trial (for either eye) with antiangiogenic drugs; use of any other investigational drugs at the time of screening, or within 30 days or 5 half-lives of screening; prior treatment in the study eye with verteporfin, external-beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy, or transpupillary thermotherapy; operative intervention for AMD in the past in the study eye; laser photocoagulation in the study eye within 1 month preceding baseline; angioid streaks or precursors of CNV in either eye due to other causes; clinically significant subretinal haemorrhage in the study eye that involved the foveal center; or any other significant clinical condition detrimental to the study outcome.
Equivalence of baseline characteristics: Yes</td></tr>
<tr><td>Interventions</td><td>Eligible patients were randomly assigned in a 1:1:1 ratio to any of the following 3 double-masked treatment arms : loading doses of 3 initial monthly intravitreal injections of 0.3 mg (intervention 1)or 0.5 mg (intervention 2) ranibizumab followed by quarterly injections of the respective doses at months 5, 8, and 11 (i.e., a total of 6 injections) or 0.3 mg ranibizumab administered monthly from baseline to month 11 (arm C, active control) (i.e., a total of 12 injections).
Intervention 1: intravitreal ranibizumab (0.3 mg) quarterly
Intervention 2: intravitreal ranibizumab (0.5 mg) quarterly
Intervention 3: intravitreal ranibizumab (0.3 mg) monthly
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention3</th></tr>
<tr><td>Agent</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>0.3mg</td><td>0.5mg</td><td>0.3mg</td></tr>
<tr><td>Frequency</td><td>quarterly</td><td>quarterly</td><td>monthly</td></tr>
</table>
Follow-up: 1 year</td></tr>
</table>

	Frequency of assessments for retreatment: monthly
Outcomes	**Primary outcome,** as defined: best-corrected visual acuity (BCVA) **Secondary outcomes**, as defined: fluid and foveal thickness on spectral-domain OCT **Adverse events**: Yes **Intervals at which outcome assessed:** Monthly

Results

Visual acuity (12 months) (intent to treat)

	Ranibizumab (n=120)	Ranibizumab (n=118)	Ranbiziumab (n=115)
Dose	0.3mg	0.5mg	0.3mg
Frequency	quarterly	quarterly	monthly
Gain of ≥15 letters, n (%)	17 (14.2)	21 (17.8)	33 (28.7)
Lost <15 letters, n(%)	112(93.3)	108(91.5)	109(94.8)
Mean change, letter (SD)	4.0 (14.88)	2.8 (13.78)	8.0 (11.27)

Adverse event

	Ranibizumab (n=120)	Ranibizumab (n=118)	Ranbiziumab (n=115)
Dose	0.3mg	0.5mg	0.3mg
Frequency	quarterly	quarterly	monthly
Eye pain	22(18.3)	14(11.9)	24(20.9)
Conjunctival haemorrhage	23(19.2)	19(16.1)	12(10.4)
Reduced VA	16(13.3)	19(16.1)	9(7.8)
Increased intraocular pressure >10 mmHg	6(5.0)	7(5.9)	17(14.8)
Non-ocular, nasopharyngitis	11(9.2)	4(3.4)	8(7.0)
Non-ocular, hypertension	10(8.3)	6(5.1)	8(7.0)

Notes

Full study name: not reported
Trial registration: NCT00275821
Funding sources: Novertis Pharma, AG, Switzerland
Declarations of interest: not reported
Study period: Jan 2006 to Feb 2011

	Subgroup analyses: none reported
Comments	**Missing data handling/loss to follow up:** 304 patients completed the study including 106 (88.3%) in the ranibizumab 0.3mg quarterly, 95(80.5%) in ranibizumab 0.5mg quarternly, and 103 (89.6%) in the ranibizumab 0.3mg monthly. ITT analysis was reported.
	Was allocation adequately concealed? unclear
	Was knowledge of the allocated intervention adequately prevented during the study? unclear
	Was the allocation sequence adequately generated? unclear
	Was the study apparently free of other problems that could put it at a high risk of bias? None observed
	Were incomplete outcome data adequately addressed? The primary end point was analysed for both per protocol and intent-to-treat (ITT) population. The PP population was a subset of the ITT population and included patients who had an assessment for BCVA at month 12 and with no major study protocol deviation. The ITT population comprised all randomised patients.
	Are reports of the study free of suggestion of selective outcome reporting? Results were reported for primary and secondary outcomes specified in the Methods section

Bibliographic reference	**VIEW 2** Heier JS, Brown DM, Chong V, Korobelnik J-F, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 2012;119(12):2537-48.
Methods	**Study design:** parallel-group randomized controlled trial **Number randomly assigned**: 2457 total participants (2457 eyes) · 615 in the aflibercept 0.5 mg every 4 weeks group · 617 in the aflibercept 2.0 mg every 4 weeks group · 616 in the aflibercept 2.0 mg every 8 weeks group · 609 in the ranibizumab group **Exclusions after randomization:** Full analysis - 45 total participants:

	· 18 in the aflibercept 0.5 mg every 4 weeks group · 4 in the aflibercept 2.0 mg every 4 weeks group · 9 in the aflibercept 2.0 mg every 8 weeks group · 14 in the ranibizumab group **Safety analysis - 38 total participants:** · 14 in the aflibercept 0.5 mg every 4 weeks group · 4 in the aflibercept 2.0 mg every 4 weeks group · 6 in the aflibercept 2.0 mg every 8 weeks group · 14 in the ranibizumab group **Losses to follow-up:** 251 participants discontinued treatment at 1-year follow-up · 75 in the aflibercept 0.5 mg every 4 weeks group · 53 in the aflibercept 2.0 mg every 4 weeks group · 63 in the aflibercept 2.0 mg every 8 weeks group · 60 in the ranibizumab group **Number analyzed:** Full analysis - 2412 total participants at 1-year follow-up · 597 in the aflibercept 0.5 mg every 4 weeks group · 613 in the aflibercept 2.0 mg every 4 weeks group · 607 in the aflibercept 2.0 mg every 8 weeks group · 595 in the ranibizumab group Safety analysis - 2419 total participants at 1-year follow-up · 601 in the aflibercept 0.5 mg every 4 weeks group · 613 in the aflibercept 2.0 mg every 4 weeks group · 610 in the aflibercept 2.0 mg every 8 weeks group · 595 in the ranibizumab group **Unit of analysis:** individual (1 study eye per participant) **How were missing data handled**? missing values imputed using last observation carried forward approach **Power calculation**: none reported

Participants	**Country:** Argentina; Australia; Austria; Brazil; Belgium; Colombia; Czech Republic; France; Germany; Hungary; India; Israel; Italy; Japan; Latvia; Mexico; Netherlands; Poland; Portugal; South Korea; Singapore; Slovakia; Spain; Sweden; Switzerland; United Kingdom (172 study sites) **Mean age** (range not reported): 78 years in the aflibercept 0.5 mg every 4 weeks group, 78 years in the aflibercept 2.0 mg every 4 weeks group, 78 years in the aflibercept 2.0 mg every 8 weeks group, and 78 years in the ranibizumab group and 75 years in the aflibercept 0.5 mg every 4 weeks group, 74 years in the aflibercept 2.0 mg every 4 weeks group, 74 years in the aflibercept 2.0 mg every 8 weeks group, and 73 years in the ranibizumab group **Gender:** 134 men (44.5%) and 167 women (55.5%) in the aflibercept 0.5 mg every 4 weeks group, 110 men (36.2%) and 194 women (63.8%) in the aflibercept 2.0 mg every 4 weeks group, 123 men (40.9%) and 178 women (59.1%) in the aflibercept 2.0 mg every 8 weeks group, and 132 men (43.4%) and 172 women (56.6%) in the ranibizumab group and 149 men (50.3%) and 147 women (49.7%) in the aflibercept 0.5 mg every 4 weeks group, 133 men (43.0%) and 176 women (57.0%) in the aflibercept 2.0 mg every 4 weeks group, 131 men (42.8%) and 175 women (57.2%) in the aflibercept 2.0 mg every 8 weeks group, and 122 men (41.9%) and 169 women (58.1%) in the ranibizumab group **Inclusion criteria:** 50 years of age or older; diagnosed with neovascular AMD in the study eye; active subfoveal CNV lesions of any subtype (12 optic disc areas or smaller) constituting ≥ 50% of total lesion size; BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters (20/40 to 20/320 Snellen equivalent); willingness and ability to return for clinic visits and complete study-related procedures; ability to provide informed consent **Exclusion criteria**: prior or concomitant treatment for AMD in the study eye; prior treatment with anti-VEGF therapy; subretinal hemorrhage or scar or fibrosis constituting > 50% of total lesion size or involving the center of the fovea in the study eye; retinal pigment epithelial tears or rips involving the macula in the study eye; history of other ocular conditions such as vitreous hemorrhage, retinal detachment, macular hole, corneal transplant, corneal dystrophy, diabetic retinopathy, diabetic macular edema, uveitis, scleromalacia; presence of other ocular conditions such as uncontrolled glaucoma, significant media opacities, phakia or pseudophakia with absence of posterior capsule, intraocular inflammation or infection; prior vitrectomy, trabeculectomy, or other filtration surgery or therapy in the study eye **Equivalence of baseline characteristics**: yes; "Baseline demographics and disease characteristics were evenly balanced among all treatment groups"
Interventions	**Intervention 1**: intravitreal aflibercept 0.5 mg every 4 weeks **Intervention 2**: intravitreal aflibercept 2.0 mg every 4 weeks

Intervention 3: intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial doses at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8)
Intervention 4: intravitreal ranibizumab 0.5 mg every 4 weeks

	Intervention1	Intervention2	Intervention3	Intervention4
Agent	aflibercept	aflibercept	aflibercept	ranibizumab
Dose	0.5mg	2.0mg	2.0mg	0.5mg
Frequency	Every 4 weeks	Every 4 weeks	Every 8 weeks after 3 initial doses, sham injections were given at the interim 4-weeks visits after week8	Every 4 weeks

Length of follow-up: 1 year for primary end point; dosing for all groups changed to as needed (PRN) after 1 year and follow-up at 2 years from baseline

Outcomes

Primary outcome, as defined in study reports: "proportion of patients maintaining vision at week 52 (losing < 15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart)"
Secondary outcomes, as defined in study reports: change in BCVA and anatomic measures, proportion gaining ≥ 15 letters, change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25) score, change in CNV area on fluorescein angiography, retinal thickness and persistent fluid as assessed by OCT, mean number of intravitreal injections, adverse events
Intervals at which outcomes assessed: every 4 weeks through 96 weeks; week 1 after first treatment for safety assessment; weeks 12, 24, 36, and 52 for the NEI-VFQ-25 assessment

Notes

Type of study reports: published journal articles; clinical trial registration
Funding sources: "Sponsored by Regeneron Pharmaceuticals, Inc, Tarrytown, New York, and Bayer HealthCare, Berlin Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript"

	Disclosures of interest: "J.S.H. is a consultant to and has received research funding from Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, and Regeneron Pharmaceuticals. He has also received travel support from Regeneron Pharmaceuticals. D.M.B. is a consultant to Alimera, Allergan, Bayer, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, and Thrombogenics and has received research funding from Alcon, Alimera, Allergan, Eli Lilly, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, and Thrombogenics. He has also received travel support from Regeneron Pharmaceuticals and lecture fees from Genentech. V.C. is a consultant to Alimera and Bayer and has received research funding from Alcon, Allergan, Bayer, Novartis, and Pfizer. He is an advisory board member for Allergan and Novartis and has also received travel support from Bayer. J.-F.K. is a consultant to Alcon, Bayer, and Thea and an advisory board member for Allergan, Bayer, and Novartis. He has received travel support from Regeneron Pharmaceuticals. P.K.K. is a consultant to Bayer, Genentech, Novartis, and Regeneron Pharmaceuticals. He has received research funding from Regeneron Pharmaceuticals. Q.D.N. is a consultant to Bausch & Lomb and Santen and has received research funding from Genentech, Novartis, and Pfizer. B.K. has received travel support from Bayer. A.H. is a consultant to Alcon, Allergan, Centocor, Johnson & Johnson, Neovista, Merck, Ophthotech, Oraya, Paloma, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Thrombogenics. He has received research funding and lecture fees from Alcon, Allergan, Genentech, Neovista, Ophthotech, Oraya, P.R.N., Q.L.T., Regeneron Pharmaceuticals, and Second Sight. Y.O. is a consultant to Alcon and Bayer and has received travel support from Bayer. G.D.Y., N.S., R.V., A.J.B., and Y.S. are employees of Regeneron Pharmaceuticals. M.A., G.G., B.S., and R.S. are employees of Bayer HealthCare. C.S.'s institution has received payments from the Medical University of Vienna for data monitoring/reviewing and statistical analysis. U.S.-E. is a consultant to Alcon, Allergan, Bayer HealthCare, and Novartis, and an advisory board member for Alcon and Novartis. She has received travel support from Bayer HealthCare and lecture fees from Bayer HealthCare and Novartis" **Study period**: March 2008 to September 2010 **Subgroup analyses**: yes; Japanese subgroup

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was unclear. "Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system"

Allocation concealment (selection bias)	Low risk	Central randomization: “Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system”
Masking of participants and personnel (performance bias)	Low risk	“Patients were masked as to treatments. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose...All other study site personnel were masked to treatment assignment by separating study records or masked packaging”
Masking of outcome assessment (detection bias)	Low risk	“A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment”
Incomplete outcome data (attrition bias)	Low risk	A full analysis set and a per protocol set were reported. Last observation carried forward (LOCF) approach was used to impute missing values; 88.1% to 91.1% of participants per treatment group completed 52 weeks of follow-up
Selective reporting (reporting bias)	Low risk	Study was registered at clinicaltrials.gov; intended outcomes were reported
Other bias	High risk	Many authors are employees of, consultants to, or have received research funding from Regeneron Pharmaceuticals, which manufactures aflibercept and participated in the design of the trial, collected and analyzed data, and prepared the study reports

Bibliographic reference	**El-Mollayess 2012** El-Mollayess GM, Mahfoud Z, Schakal AR, Salti HI, Jaafar D, Bashshur ZF. Fixed-interval versus OCT-guided variable dosing of intravitreal bevacizumab in the management of neovascular age-related macular degeneration: A 12-month randomized prospective study. American Journal of Ophthalmology 2012;153(3):481-9.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group):** 120 total participants; 60 participants in each group **Exclusions after randomization**: none reported

<table>
<tr><td></td><td>Number analyzed (total and per group): 120 participants; 60 participants in each group
Unit of analysis: individual (one study eye per participant)
Losses to follow up: none reported
Intention to treat analysis: all participants randomized were analysed
Power calculation: “detect a difference of at least 5 letters in mean visual acuity using the independent t test with 80% power and an alpha level of 5%, assuming a standard deviation of 10 letters, 60 eyes were needed in each group”
Study design comment: “If both eyes of the same patient were eligible, then the eye with the worse visual acuity was enrolled.”</td></tr>
<tr><td>Participants</td><td>Country: France and Lebanon
Mean age: 77 years
Gender (percent): 78 women and 42 men
Inclusion criteria: “1) age 50 years or older; 2) subfoveal choroidal neovascularization (CNV) attributable to AMD diagnosed by fluorescein angiography (FA); 3) presence of subretinal fluid, cystic maculopathy, or central retinal thickness >250 ?m on OCT; 4) best-corrected vision, using ETDRS charts, be- tween 20/40 and 20/400 (Snellen equivalent); 5) CNV less than 5400 µm in greatest linear dimension; and 6) ability to understand and sign a consent form."
Exclusion criteria: “1) presence of subfoveal scarring or hemorrhage; 2) media opacity that would prevent good- quality retinal imaging; 3) history of uveitis, vitrectomy, diabetic retinopathy, or other condition that may affect vision; and 4) thromboembolic event less than 6 months prior to enrollment.
Equivalence of baseline characteristics: baseline characteristics by group not reported</td></tr>
<tr><td>Interventions</td><td>Intervention: intravitreal 1.25 mg bevacizumab injection (Avastin; Roche, Basel, Switzerland)
Treatment schedule 1: PRN (variable dosing)
Treatment schedule 2: every 4 to 6 weeks (lfixed-interval dosing)
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25</td><td>1.25</td></tr>
<tr><td>Frequency</td><td>PRN (variable dosing)</td><td>Every 4 to 6 weeks (fixed interval dosing)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>Follow-up: 12 months
Frequency of assessments for retreatment: every 4 to 6 weeks</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: improvement in BCVA and CRT at 12 months
Secondary outcomes, as defined: none reported
Adverse events: ocular and systemic adverse events
Review outcomes not reported: mean change in CRT, quality of life, cost
Intervals at which outcome assessed: every 4 to 6 weeks</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)
<table>
<tr><td>Agent</td><td>Bevacizumab (n=59)</td><td>Bevacizumab (n=60)</td><td>RR (95%CI)</td></tr>
<tr><td>Dose</td><td>1.25</td><td>1.25</td><td></td></tr>
<tr><td>Frequency</td><td>PRN (variable dosing)</td><td>Every 4 to 6 weeks (fixed interval dosing)</td><td></td></tr>
<tr><td>Gain of ≥15 letters, n(%)</td><td>24 (40)</td><td>21 (35)</td><td>1.16 (0.73, 1.85)</td></tr>
<tr><td>Mean BCVA letters</td><td>64.3</td><td>65.8</td><td></td></tr>
</table>
Adverse event (12 months)
No severe ocular adverse events were noted in both groups over 12 months. Similarly no systemic adverse events were reported. However, 3 months after the completion of the study, 5 patients in the fixed-interval dosing group had major thromboembolic events.

Number of injections (12 months)
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25</td><td>1.25</td></tr>
<tr><td>Frequency</td><td>PRN (variable dosing)</td><td>Every 4 to 6 weeks (fixed interval dosing)</td></tr>
<tr><td>Mean number of injections</td><td>3.8</td><td>9.5</td></tr>
</table></td></tr>
<tr><td>Notes</td><td>Full study name: not reported</td></tr>
</table>

	Trial registration: not reported **Funding sources**: Department of Ophthalmology and University Research Board of American University of Beirut Medical Center, Beirut, Lebanon **Declarations of interest**: "The authors indicate no financial interest in any product discussed in this study" **Study period**: May 2009 to October 2009 **Subgroup analyses**: none reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization program (GraphPad StatMate, version 1.01i; GraphPad Software Inc, San Diego, California, USA) "
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants (performance bias)	High risk	"visual acuity examiners were masked to treatment regimen and patients were instructed not to share this information with the examiner " "Treating physicians were not masked to the treatment regimen of patients under their care and no sham injections were employed."
Masking of outcome assessment (detection bias)	Low risk	"visual acuity examiners were masked to treatment regimen and patients were instructed not to share this information with the examiner" "The physician reviewing OCT images or other material to be recorded in the study was masked to that particular patient's identity and treatment regimen and in no way could be involved in the treatment of that patient."
Incomplete outcome data (attrition bias)	Low risk	"All patients completed the 12 months of the study and were able to make scheduled visits with no greater than a 7-day delay".
Selective reporting (reporting bias)	Unclear risk	Trial registry and citation to protocol not reported.
Other bias	Low risk	None identified

Bibliographic reference	**GMAN 2015** Mahmood S, Roberts SA, Aslam TM, Parkes J, Barugh K, Bishop PN. Routine versus as-needed bevacizumab with 12-weekly assessment intervals for neovascular age-related macular degeneration: 92-week results of the GMAN Trial. Ophthalmology 2015;122(7):1348-55.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group):** 331 total participants; 166 participants in PRN group, 50 participants in routine group **Exclusions after randomization:** withdrew PRN -48, withdrew ROUTINE – 22 **Number analyzed (total and per group**): PRN-166, ROUTINE-165 **Unit of analysis:** individual (one study eye per participant) **Losses to follow up**: PRN-26, ROUTINE-22 **Compliance**: completed trial – PRN-140, ROUTINE-143 **Intention to treat analysis:** PRN-166, ROUTINE-165 **Power calculation:** Yes, a noninferiority margin of 4 to 5 letters at 90% power for the sample size planned for the study **Study design comment:** none
Participants	**Country:** UK **Median age**: 80 years **Gender (percent):** 61% women and 39% men **Inclusion criteria:** age more than 50 years with a diagnosis of nAMD and a best-corrected visual acuity (BCVA) of logarithm of the minimum angle of resolution 0.3 to 1.2 **Exclusion criteria:** "lesion showed signs of >50% fibrosis, hemorrhage, or serous pigment epithelial detachment. Patients with a medical history of myocardial infarction, cardiovascular accident, or gastrointestinal perforation were excluded when the trial commenced. However, as more evidence emerged suggesting a low systemic risk from the intravitreal use of anti-VEGF drugs, the protocol was amended so that myocardial infarction and gastrointestinal perforation were not used as exclusion criteria, and only patients with a history of cerebrovascular accident within 6 months were excluded." **Equivalence of baseline characteristics:** Yes, there were no substantial imbalances in the ocular or demographic characteristics between the 2 groups of the study

<table>
<tr><td>Interventions</td><td>
Intervention: intravitreal 1.25 mg bevacizumab injection (Avastin; Roche, Basel, Switzerland)
Treatment schedule 1: 3 monthly loading doses, then PRN (PRN treatment)
Treatment schedule 2: 3 monthly loading doses, then every 12 weeks (routine treatment)
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td></tr>
<tr><td>Frequency</td><td>3 monthly loading doses, then PRN</td><td>3 monthly loading doses, then every 12 weeks (routine treatment)</td></tr>
</table>
Follow-up: 92 weeks
Frequency of assessments for retreatment: every 12 weeks
</td></tr>
<tr><td>Outcomes</td><td>
Primary outcome, as defined: mean BCVA at 92 weeks
Secondary outcomes, as defined: change in mean visual acuity from baseline to 92 weeks and the percentages of patients who had a change in visual acuity from baseline of ≥5, ≥10, or ≥15 letters, comparing contrast sensitivity, reading speed, and central macular thickness between the 2 arms at 92 weeks
Adverse events: Yes
Intervals at which outcome assessed: every 12 weeks for 92 weeks
</td></tr>
<tr><td>Results</td><td>
Visual acuity (92 weeks)
<table>
<tr><td>Agent</td><td>Bevacizumab (n=166)</td><td>Bevacizumab (n=165)</td><td>RR (95%CI)</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td><td></td></tr>
<tr><td>Frequency</td><td>3 monthly loading doses, then PRN</td><td>3 monthly loading doses, then every 12 weeks (routine treatment)</td><td></td></tr>
<tr><td>Gain of ≥15 letters, n (%)</td><td>22(13)</td><td>40 (24)</td><td>0.55 (0.34, 0.88)</td></tr>
<tr><td>Loss of ≥15 letters, n (%)</td><td>27(16)</td><td>13 (8)</td><td>2.06 (1.10, 3.86)</td></tr>
<tr><td>Gain of ≥5 letters, n (%)</td><td>68(41)</td><td>86 (52)</td><td>0.79 (0.62, 0.99)</td></tr>
</table>
</td></tr>
</table>

Loss of ≥5 letters, n (%)	63(38)	33(20)	1.90 (1.32, 2.73)
Mean change in BCVA, letters (SD)	52.8 (19.4)	57.2 (17.6)	

Adverse events (92 weeks)

Agent	Bevacizumab (n=166)	Bevacizumab (n=165)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	3 monthly loading doses, then PRN	3 monthly loading doses, then every 12 weeks (routine treatment)	
Uveitis	2	3	0.66 (0.11, 3.91)
Vitreous haemorrhage	1	1	0.99 (0.06, 15.76)
Cataract surgery	13	13	0.99 (0.48, 2.08)
Death any cause	12	10	1.19 (0.53, 2.68)
Gastrointestinal	8	6	1.33 (0.47, 3.74)
Infection	2	1	1.99 (0.18, 21.71)

Number of injections (92 weeks)

Agent	Bevacizumab	Bevacizumab
Dose	1.25mg	1.25mg
Frequency	3 monthly loading doses, then PRN	3 monthly loading doses, then every 12 weeks (routine treatment)
Mean number of injection	9.1	10.8

Notes	**Full study name: The** Greater Manchester Avastin for Neovascularisation Study Trial registration: ISRCTN 34221234 and EudraCT number 2007-003853-97

	Funding sources: “Supported by Greater Manchester Primary Care Trusts, National Health Service, England, and Manchester Biomedical Research Centre.” **Declarations of interest:** "The author(s) have made the following disclosure(s): S.M.: Advisory boards of and financial support _ Novartis and Bayer. T.M.A: Advisory boards of and financial support _ Novartis and Bayer." **Study period:** February 2008 to May 2013 **Subgroup analyses**: none reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	“Computer-generated allocation lists were drawn up by the trial statistician using block randomization with a variable block size.”
Allocation concealment (selection bias)	Low risk	“Computer-generated allocation lists were drawn up by the trial statistician using block randomization with a variable block size.”
Masking of participants (performance bias)	High risk	“patients, treating clinicians, and other staff involved in the study were not masked
Masking of outcome assessment (detection bias)	Low risk	“The optometrists who measured BCVA, reading speed, and contrast sensitivity were masked to the study arm;”
Incomplete outcome data (attrition bias)	Low risk	An intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	Compared with the trial registries, there does not appear to be selective outcome reporting
Other bias	Unclear risk	The study was not powered to investigate safety

Bibliographic reference	**HABOUR 2013** Busbee BG, Ho AC, Brown DM, Heier JS, Suner IJ, Li Z, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120(5):1046-56.
Methods	**Study design**: parallel-group randomized controlled trial

	Number randomized (total and per group): Total: 1098 0.5 mg monthly: 276 0.5 mg PRN: 275 2.0 mg monthly: 274 2.0 mg PRN: 273 **Exclusions after randomization**: 1 patient was randomized before screen failure, and no baseline or post-baseline data were reported for this patient; therefore, the patient was excluded from analysis **Number analyzed (total and per group): Total: 1098** 0.5 mg monthly: 275 0.5 mg PRN: 275 2.0 mg monthly: 274 2.0 mg PRN: 273 **Unit of analysis:** individual (one study eye per participant) **Losses to follow up**: Discontinued study 0.5 mg monthly: 2 0.5 mg PRN: 2 2.0 mg monthly: 2 2.0 mg PRN: 2 Discontinued treatment 0.5 mg monthly: 2 0.5 mg PRN: 2 2.0 mg monthly: 3 2.0 mg PRN: 3 **Compliance**: Not reported **Intention to treat analysis:** Yes **Reported power calculation:** Yes, 80% power in the intention-to-treat analysis for the 3 primary comparisons **Study design comment**: None
Participants	**Country**: 100 study centers across the United States **Age**: 0.5 mg monthly mean age=78.8±8.4 (range 53.0-97.0), 0.5 mg PRN mean age=78.5±8.3 (range 53.0-97.0), 2.0 mg monthly mean age=79.3±8.3 (range 50.0-96.0), 2.0 mg PRN mean age=78.3 (range=54.0-98.0)

<table>
<tr><td></td><td>Gender (percent): 0.5 mg monthly 113(41.1%) men and 162 (58.9%) women, 0.5 mg PRN 112 (40.7%) men and 163 (59.3%) women, 2.0 mg monthly 104 (38.0%) men and 170 (62.0%) women, 2.0 mg PRN 117 (42.9%) men and 156 (57.1%) women
Inclusion criteria: aged 50 years or older and fulfilled the following inclusion criteria for the study eye: (1) BCVA of 20/40 to 20/320 (Snellen equivalent), using ETDRS charts (at a distance of 4 meters); (2) active subfoveal lesions with classic CNV, some classic CNV component, or purely occult CNV; (3) total area of lesion 12 disc areas (DA) or 30.48 mm2; and (4) total CNV area constitutes 50% of total lesion area based on fluorescein angiography (FA). For the inclusion of purely occult or occult with some classic CNV, activity of the lesion had to be demonstrated by one of several criteria. This included a 10% increase in CNV lesion size on interval visits, a documented visual loss of 1 line of Snellen vision, or the presence of hemorrhage at presentation
Exclusion criteria: a history of vitrectomy surgery; prior treatment with photodynamic therapy with verteporfin, external beam radiation therapy, or transpupillary thermotherapy; previous intravitreal drug delivery; previous subfoveal laser photocoagulation; uncontrolled blood pressure; atrial fibrillation not managed by the patient's primary care physician or cardiologist within 3 months of the screening visit; or a history of stroke within 3 months of the screening visit.
Equivalence of baseline characteristics: Yes, "All variables were well balanced among the 4 treatment groups."
Diagnoses in participants: approximately 46% of patients had minimally classic CNV lesions, 16% had predominantly classic lesions, and 38% had purely occult CNV</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 0.5 mg ranibizumab monthly
Intervention 2: 0.5 mg ranibizumab PRN
Intervention 3: 2.0 mg ranibizumab monthly
Intervention 4: 2.0 mg ranibizumab PRN
<table><tr><th></th><th>Intervention1</th><th>Intervention 2</th><th>Intervention3</th><th>Intervention4</th></tr><tr><td>Agent</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Ranibizumab</td><td>Ranibizumab</td></tr><tr><td>Dose</td><td>0.5mg</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td></tr><tr><td>Frequency</td><td>Monthly</td><td>PRN</td><td>Monthly</td><td>PRN</td></tr></table>
Follow-up: 12 months
Frequency of assessments for retreatment: at month 3 visit and thereafter</td></tr>
</table>

<table>
<tr><td>Outcomes</td><td>Primary outcome, as defined: mean change from baseline in BCVA at month 12
Secondary outcomes, as defined: mean number of ranibizumab injections up to, but not including, month 12; the mean change from baseline in central foveal thickness (CFT) based on SD-OCT over time to month 12; the proportion of patients who gained 15 letters from baseline in BCVA at month 12; and the proportion of patients with a Snellen
Adverse events (Y/N) Yes
Intervals at which outcome assessed: Safety and ocular parameters were assessed on day 7; subsequently, all patients had scheduled monthly visits for evaluation of safety and efficacy. Fluorescein angiography and fundus photography were per- formed at screening and at months 3, 6, and 12.</td></tr>
<tr><td>Results</td><td>Visual acuity (12 months)
<table>
<tr><td></td><td>Ranibizumab (n=275)</td><td>Ranibizumab (n=275)</td><td>Ranibizumab (n=274)</td><td>Ranibizumab (n=273)</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td></tr>
<tr><td>Frequency</td><td>Monthly</td><td>PRN</td><td>Monthly</td><td>PRN</td></tr>
<tr><td>Gain of ≥15 letters, n(%)</td><td>95 (34.5)</td><td>83 (30.2)</td><td>99 (36.1)</td><td>90 (33.0)</td></tr>
<tr><td>Loss of ≥15 letters</td><td>6</td><td>15</td><td>18</td><td>14</td></tr>
<tr><td>Gain or loss between 14 letters</td><td>174</td><td>177</td><td>157</td><td>169</td></tr>
</table>
Adverse events (12 months)
<table>
<tr><td></td><td>Ranibizumab (n=274)</td><td>Ranibizumab (n=275)</td><td>Ranibizumab (n=274)</td><td>Ranibizumab (n=272)</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>0.5mg</td><td>2.0mg</td><td>2.0mg</td></tr>
<tr><td>Frequency</td><td>Monthly</td><td>PRN</td><td>Monthly</td><td>PRN</td></tr>
<tr><td>Any SAE</td><td>3</td><td>3</td><td>6</td><td>1</td></tr>
<tr><td>Endophthalmitis</td><td>2</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Reduced VA</td><td>0</td><td>1</td><td>1</td><td>1</td></tr>
</table></td></tr>
</table>

Death any cause	8	4	5	5
Nonfatal myocardial infarction	4	0	2	4
Gastrointestinal perforation	0	0	1	0

Number of injections (12 months)

Agent	Ranibizumab	Ranibizumab	Ranibizumab	Ranibizumab
Dose	0.5mg	0.5mg	2.0mg	2.0mg
Frequency	Monthly	PRN	Monthly	PRN
Mean number of injections (SD)	11.3 (1.8)	7.7 (2.7)	11.2 (2.1)	6.9 (2.4)

Notes

Full study name: Not reported
Type of study: published
Trial registration: NCT00891735
Funding sources: Genentech, Inc. (South San Francisco, CA) provided support for the study and participated in the study design; conducting the study; and data collection, management, and interpretation.
Declarations of interest: B.G.B. has served as a consultant for Alimera, Elan, Genentech, Synergetics, and Thrombogenics; has received research funding from Genentech; is a member of the speakers bureau for Genentech and Regeneron; and has received royalties from AKORN. A.C.H. has served as a consultant for Alcon, Allergan, Centocor/Johnson & Johnson, Genentech, Merck, NeoVista, Ophthotech, Oraya, Paloma, PRN, QLT, Regeneron, and Thrombogenics; has received research funding from Alcon, Allergan, Genentech, National Eye Institute/ National Institutes of Health, NeoVista, Ophthotech, Oraya, PRN, QLT, Regeneron, and Second Sight; and is a member of the speakers bureau for Alcon, Genentech, and Regeneron. D.M.B. has served as a consultant for Alcon, Alimera, Allergan, Genentech, Novartis, Regeneron, and Thrombogenics; has received research funding from Abbott, Alcon, Alimera, Allergan, Eli Lilly, Genentech, GlaxoSmithKline, Ophthotech, Novartis, Regeneron, and Thrombogenics; and is a member of the speakers

	bureau for Genentech and Regeneron. J.S.H. has served as a consultant for Acucela, Allergan, Bayer, Forsight, Fovea, Genentech, Genzyme, GlaxoSmithKline, LPath, Neovista, Oraya, Paloma, QLT, Quark, and Regeneron; and has received research funding from Alcon, Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, Neurotech, Novartis, Ophthalmic Consultants of Boston, Ophthotech, Paloma, and Regeneron. I.J.S. has served as a consultant for Genentech, Eyetech, Regeneron, and Thrombogenics; has received research funding from Genentech; is a mem- ber of the speakers bureau for Genentech, Optos, and Regeneron; and is a board member of Optos. Z.L., R.G.R., and P.L. are employees of Genen- tech. Support for third-party writing assistance for this manuscript provided by Linda Merkel, PhD, and Michelle Kelly, PhD, of UBC-Envision Group, and was provided by Genentech, Inc. **Study period:** recruitment from July 2009 and August 2010 **Reported subgroup analyses:** No

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“each patient received a computer-generated subject number on day 0, which randomly assigned patients in a 1:1:1:1 ratio to 1 of 4 ranibizumab treatment groups: 0.5 mg monthly, 0.5 mg PRN, 2.0 mg monthly, and 2.0 mg PRN"
Allocation concealment (selection bias)	Low risk	“Randomization was stratified by VA at day 0 (≤54 letters [approximate Snellen equivalent <20/80] vs. ≥55 letters [approximate Snellen equivalent ≥20/80]), CNV classification at baseline (predominantly classic, minimally classic, or purely occult), and study center.”
Masking of participants (performance bias)	Unclear risk	“All study site personnel, the designated physician(s), central reading center personnel, patients, and the sponsor and its agents were masked to treatment drug dose assignment (0.5 mg vs. 2.0 mg). Treatment frequency (ie, monthly vs. PRN dosing) was not masked to patient and site personnel”
Masking of outcome assessment (detection bias)	Unclear risk	“All study site personnel, the designated physician(s), central reading center personnel, patients, and the sponsor and its agents were masked to treatment drug dose assignment (0.5 mg vs. 2.0 mg). Treatment frequency (ie, monthly vs. PRN dosing) was not masked to patient and site personnel”
Incomplete outcome data (attrition bias)	Low risk	An intention-to-treat analysis was used.

Selective reporting (reporting bias)	Low risk	Compared with the trial registry, there does not appear to be selective outcome reporting.
Other bias	Low risk	None identified

Bibliographic reference	**CATT 2011** CATT Research Group; Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2011;364(20):1897-908.
Methods	**Number randomized (total and per group):** 1208 participants randomly assigned to study treatment; number of participants randomized per group not reported **Exclusions after randomization**: one study center (23 participants) was excluded due to protocol violations **Number analyzed (total and per group):** 1105 total participants; 265 in bevacizumab monthly group, 284 in ranibizumab monthly group, 271 in bevacizumab as needed group, and 285 in ranibizumab as needed group **Unit of analysis**: individuals (one study eye per participant) **Losses to follow up**: 80 total participants: 21 in bevacizumab monthly group (4 died and 17 with missing data), 17 in ranibizumab monthly group (4 died and 13 with missing data), 29 in bevacizumab as needed group (11 died and 18 with missing data), 13 in ranibizumab as needed group (5 died and 8 with missing data) **Compliance**: limited information given: mean of 11.9 treatments given for bevacizumab monthly group and mean of 11.7 treatments given for ranibizumab monthly group **Intention to treat analysis**: no, 103 participants enrolled and randomized were not included in the analyses **Reported power calculation:** yes, sample of 277 participants per group for power of 90% **Study design comment:** non-inferiority design, four arms, six pairwise comparisons planned; at one year, participants in the monthly dose treatment groups were re-randomized to either continue with monthly injections or switch to as needed injections of the same treatment drug
Participants	**Country**: USA **Age**: mean was 80 years in bevacizumab monthly group, 79 years in ranibizumab monthly group, 79 years in bevacizumab as needed group, and 78 years in ranibizumab as needed group **Gender (percent):** 732/1185 (61.8%) women and 453/1185 (38.2%) men

<table>
<tr><td></td><td>Inclusion criteria: age 50 years or older; one study eye per participant with untreated active CNV due to AMD (based on presence of leakage as seen by fluorescein angiography and of fluid as seen by OCT); VA of 20/25 to 20/320 on electronic visual-acuity testing
Exclusion criteria: fibrosis or atrophy in center of fovea in the study eye; CNV in either eye due to other causes; retinal pigment epithelial tear involving the macula; any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention or contribute to VA loss during the 3 year follow-up period; active or recent (within 4 weeks) intraocular inflammation; current vitreous hemorrhage in the study eye; history of rhegmatogenous retinal detachment or macular hole; active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis; spherical equivalent > 8 diopters; intraocular surgery (including cataract surgery) in the study eye within 2 months; uncontrolled glaucoma; participants unable to be photographed to document CNV due to known allergy to fluorescein dye, lack of venous access or cataract obscuring the CNV; premenopausal women not using adequate contraception; pregnancy or lactation; history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications; current treatment for active systemic infection; uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders; history of recurrent significant infections or bacterial infections; inability to comply with study or follow-up procedures
Equivalence of baseline characteristics: a slightly higher percentage of participants in bevacizumab monthly group had history of transient ischemic attack (8.7% compared with 4% in ranibizumab monthly group, 4% in ranibizumab as needed group, and 6.3% in bevacizumab as needed group)</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg bevacizumab injections on
Intervention 2: 0.5 mg intravitreal ranibizumab injections
Treatment schedule 1: PRN
Treatment schedule2: every 4 weeks for first year, then re-randomization to injections PRN or every 4 weeks

<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention3</th><th>Intervention4</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Ranibizumab</td><td>Bevacizumab</td><td>Ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td><td>1.25mg</td><td>0.5mg</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>Frequency</td><td>Every 4 weeks for 1 year, re-randomization to bevacizumab every 4 weeks or as needed</td><td>Every 4 weeks for 1 year, re-randomization to ranibizumab every 4 weeks or as needed</td><td>As needed for 2 years</td><td>As needed for 2 years</td></tr></table> **Length of follow up**: **Planned: 12 months for primary analysis**; 24 months for secondary analyses, with modifications to two intervention arms as described above Actual: 12 months for primary analysis; 24 months for secondary analyses
Outcomes	**Primary outcome**, as defined: change in visual acuity from baseline at 12 months with a non-inferiority margin of 5 letters **Secondary outcomes**: proportion of eyes with 15-letter change, number of injections, OCT measured change in foveal thickness, change in lesion size on OCT and also on fluorescein angiography, incidence of ocular and systemic adverse events, and annual drug cost **Adverse events**: ocular and systematic adverse events **Review outcome not reported**: quality of life **Intervals at which outcomes were assessed**: weeks 4, 12, 24, 36, 52 during first year for visual acuity; weeks 4, 8, 12, 24, 52 for changes on OCT
Notes	**Full study name**: Comparison of Age-related macular degeneration Treatment Trials **Type of study**: published **Funding**: National Eye Institute, National Institutes of Health, US **Declarations of interest**: one investigator reported receiving consulting fees from GlaxoSmithKline and another consulting fees from Neurotech and SurModics **Study period**: accrual February 2008 through December 2009; follow up through December 2011 **Reported subgroup analyses**: none, but risk factors for 2-year VA outcomes have been reported (Ying 2015)

Bias	Authors' judgement	Support for judgement

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

Bibliographic reference	**IVAN 2012** Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012;119(7):1399-411
Methods	**Study design:** parallel-group randomized controlled trial **Number randomized (total and per group):** **Drug randomization**: 628 total participants; 305 to bevacizumab group and 323 to ranibizumab group

	Regimen randomization: 294/305 in bevacizumab group and 312/323 in ranibizumab group completed first three injections and were randomized to continue or discontinue treatment: 149 continued bevacizumab; 145 discontinued bevacizumab; 157 continued ranibizumab; and 155 discontinued ranibizumab **Exclusions after randomization**: 18 participants did not receive treatment and were excluded after randomization to drug treatment (9 in bevacizumab group and 9 in ranibizumab group) **Number analyzed (total and per group):** at one year follow up: 561 total participants at one year; 136 in continued bevacizumab group; 138 in discontinued bevacizumab group; 141 in continued ranibizumab group; and 146 in discontinued ranibizumab group at two years follow up: 525 total participants at one year; 127 in continued bevacizumab group; 127 in discontinued bevacizumab group; 134 in continued ranibizumab group; and 137 in discontinued ranibizumab group **Unit of analysis**: individual (one study eye per participant) **Losses to follow up**: at one year follow up: 49 total participants: 4 participants receiving treatment withdrew prior to completing third injection (2 in bevacizumab group and 2 in ranibizumab group); 45 participants randomized to regimen groups exited trial before one year (13 in continued bevacizumab group; 7 in discontinued bevacizumab group; 16 in continued ranibizumab group; and 9 in discontinued ranibizumab group) at two years follow up: 85 total participants: 5 participants receiving treatment withdrew prior to completing third injection (3 in bevacizumab group and 2 in ranibizumab group); 80 participants randomized to regimen groups exited trial before two years (21 in continued bevacizumab group; 18 in discontinued bevacizumab group; 23 in continued ranibizumab group; and 18 in discontinued ranibizumab group) **Compliance:** the wrong study drug was administered twice during the first year; at one year follow up: adherence was 6576/6699 (98%) scheduled injections received at two years follow up: adherence was 12761/14640 (87%) scheduled injections received **Intention to treat analysis:** no, 67 participants enrolled and randomized were not included in the analyses at one year and 103 at two years **Reported power calculation**: yes, sample of 600 participants per group for power of 90% to detect non-inferiority **Study design comment:** non-inferiority design; 2 x 2 factorial design – randomization in two stages: first randomized to drug treatment (bevacizumab or ranibizumab), then to treatment regimen (continue monthly injections or discontinue monthly injections and switch to as needed injections given in three month cycles); results reported only as bevacizumab versus ranibizumab and continuous versus discontinuous

<table>
<tr><td>Participants</td><td>Country: UK (23 study centers)
Age: mean age for 610 participants receiving treatment was 78 years
Gender (percent): 366/610 (60%) women and 244/610 (40%) men
Inclusion criteria: age 50 years or older; previously untreated neovascular AMD in study eye with any component of the neovascular lesion (CNV, blood, serous pigment epithelial detachment, elevated blocked fluorescence) involving the center of the fovea, confirmed by fluorescein angiography; best-corrected VA of 25 letters or greater on the ETDRS chart (measured at 1 m)
Exclusion criteria: neovascular lesion of 50% or more fibrosis or blood; more than 12 disc diameters; argon laser treatment in study eye within 6 months; presence of thick blood involving the center of the fovea; presence of other active ocular disease causing concurrent vision loss; myopia 8 or more diopters; previous treatment with PDT or a VEGF inhibitor in study eye; women pregnant, lactating, or of child-bearing potential; men with a spouse or partner of child-bearing potential
Equivalence of baseline characteristics: yes</td></tr>
<tr><td></td><td>Diagnoses in participants: 301/610 (58%) had neovascular AMD with CNV in foveal center; 308/610 (54%) had fluid in foveal center; 90/610 (16%) had hemorrhage in foveal center; 75/610 (13%) had other foveal center involvement; and 15/610 (3%) had no CNV or not possible to grade</td></tr>
<tr><td>Interventions</td><td>Intervention 1: 1.25 mg in 0.05 ml intravitreal bevacizumab injected monthly for two years
Intervention 2: 0.5 mg intravitreal ranibizumab injected monthly for two years
Intervention 3: after first 3 monthly 1.25 mg intravitreal bevacizumab injections, monthly treatment was discontinued and treatment was given as needed in cycles of 3 monthly doses
Intervention 4: after first 3 monthly 0.5 mg intravitreal ranibizumab injections, monthly treatment was discontinued and treatment was given as needed in cycles of 3 monthly doses
<table>
<tr><th></th><th>Intervention1</th><th>Intervention2</th><th>Intervention3</th><th>Intervention4</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>ranibizumab</td><td>Bevacizumab</td><td>ranibizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>0.5mg</td><td>1.25mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td colspan="2">Monthly for 2 years
Monthly for 2 years</td><td colspan="2">Initial 3 doses monthly, then treatment was givens as needed in cycles of 3 monthly dose</td></tr>
</table>
</td></tr>
</table>

	Follow up: 2 years **Frequency of follow-up assessments:** monthly
Outcomes	**Primary outcome, as** defined: best-corrected distance visual acuity measured as ETDRS letters at two years **Secondary outcomes**, as defined in protocol: at 1 year and 2 years follow up - frequencies of adverse effects of treatment; generic and vision-specific health-related quality of life; treatment satisfaction; cumulative resource use/cost and cost-effectiveness; clinical measures of vision (contrast sensitivity measured with Pelli-Robson charts, near visual acuity measured by Bailey-Love near reading cards, and reading speed measured with Belfast reading charts); lesion morphology (fluorescein angiography and OCT); distance visual acuity at one year; survival free from treatment failureExploratory analysis: association between serum markers and cardiovascular serious adverse eventsIntervals at which outcomes were assessed: monthly through 24 months; various data were collected at every visit depending on assessment schedule and regimen group
Notes	**Full study name**: alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation **Type of study**: published **Funding sources**: National Institute for Health Research Health Technology Assessment program, UK **Declarations of interest:** various authors reported being principal investigators of trials sponsored by Novartis; attending and being remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan, and/or Bausch and Lomb; being employed by institution that has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and/or Pfizer; receiving honoraria from Novartis for lecture and/or teaching fees from Janssen-Cilag **Study period**: random enrollment 27 March 2008 to 15 October 2010 **Reported subgroup analyses**: 3 genetic polymorphisms (Lotery 2013) **Contacting study investigators**: trial authors not contacted as data were available in published reports

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomized allocations were computer generated by a third party in blocks and stratified by center." "Randomisation was stratified by centre and was blocked to ensure roughly equal numbers of participants per group within a centre."

Allocation concealment (selection bias)	Low risk	"Research teams at sites recruited participants, and accessed a password-protected website to randomize participants. Allocations were concealed until participants' eligibility and identities were confirmed." "Allocations were computer generated and concealed with an internet-based system (Sealed Envelope, London, UK). Staff in participating centres accessed the website and, on entering information to confirm a participant's identity and eligibility, were provided with the unique study number."
Masking of participants and personnel (performance bias)	Low risk	From study protocol: "Participants, clinicians and trial personnel will be masked to the VEGF inhibitor to which a participant is assigned." "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months." "We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments." From study protocol: "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Masking of outcome assessment (detection bias)	Low risk	"We intended that drug allocation should be concealed by having separate masked assessment and unmasked treating teams. This system was achieved by 14 sites. At the other 9 sites, staffing levels could not support this system and an unmasked staff member prepared ranibizumab in a syringe identical to those containing bevacizumab and did not perform assessments." "Lesion morphology was assessed by independent graders masked to drug and treatment regimen." From study protocol: "We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months."
Incomplete outcome data (attrition bias)	Unclear risk	67/628 (11%) participants randomized were not included in the one-year analysis; 111/628 (18%) participants randomized were not included in the two-year analysis.

Selective reporting (reporting bias)	Unclear risk	Differences between the protocol and published one-year and two-year results papers included: 1) two secondary outcomes in the protocol were not listed in paper: treatment satisfaction and survival free from treatment failure; and 2) exploratory (serum) analysis in protocol upgraded to a secondary outcome in paper
Other bias	Low risk	None observed

The Chan study described below was identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

Bibliographic reference	**Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.**
Country/ies	USA
Study type	Open label RCT
Aim of the study	This prospective study compared the outcomes of 0.5 vs 2.0mg intravitreal ranibizumab injections (RI) for treating vascularized pigment epithelial detachment (vPED) due to age-related macular degeneration.
Study dates	Published 2015
Sources of funding	Not reported
Sample size	36 eyes (36 people)
Inclusion Criteria	Eligibility criteria included: Patients were age≥50, Patients had submacular vPED due to AMD (confirmed by fundus photography (FP), fluorescein angiography (FA), and OCT) Patients had PED measuringr12 disc areas Patients had visional acuity of ETDRS BCVA letter scores of ≥19 and ≤69 (20/400 to 20/40) Patitents hadsubmacular hemorrhage or fibrosis within 50% of entire PED.
Exclusion Criteria	Patients had anti-VEGF therapy within the past 30 days; Patients had more than one prior PDT session; Patients had treatment of AMD in past 30 days; Patients had any cause of CNV and PED other than AMD; Patients had serous PED without CNV;

<table>
<tr><th>Bibliographic reference</th><td>Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.</td></tr>
<tr><td></td><td>Patients had PED with polypoidal choroidal vasculopathy (PCV).</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Ranibizumab, 0.5mg montly (n=6)</th><th>Ranibizumab, 0.5mg PRN (n=7)</th><th>Ranibizumab, 2.0mg montly (n=12)</th><th>Ranibizumab, 2.0mg PRN (n=11)</th></tr>
<tr><td>Mean age (SD)</td><td>82.0 (6.2)</td><td>84.0 (6.0)</td><td>77.3 (6.2)</td><td>74.6 (9.4)</td></tr>
<tr><td>Male: n (%)</td><td>0</td><td>1 (14.3)</td><td>5 (41.7)</td><td>4 (36.4)</td></tr>
<tr><td>Mean BCVA, letters (SD)</td><td>54.0 (6.63)</td><td>53.3 (14.4)</td><td>61.5 ((7.2)</td><td>58.5 (8.4)</td></tr>
</table>
</td></tr>
<tr><td>Study visits and procedures</td><td>Eligible patients were randomized to receive one of four treatment protocols:
Regimen (1) RI of 0.5mg monthly for 12 months,
Regimen (2) RI of 0.5mg monthly for 4 months followed by repeat RI on a PRN basis for 8 months,
Regimen (3) RI of 2.0mg monthly for 12 months
Regimen (4) RI of 2.0mg on a monthly injection for 4 months followed by repeat RI on a PRN basis.
The PRN criteria for Regimen 2 and 4 were the following:
(a) RI was continued if the macula was not completely flat on optical coherence tomography (OCT) (sensory macula and retinal pigment epithelium (RPE)).
(b) If macular flattening occurred, retreatment was allowed for the following: (i) loss of five letters on the Early Treatment of the Diabetic Retinopathy Study (ETDRS) chart compared with a prior visit;
(ii) new or persistent subretinal fluid (SRF) or cystoid macular edema (CME) on OCT; (iii) New-onset or persistent choroidal neovascularization (CNV), and
(iv) new or persistent hemorrhage.</td></tr>
<tr><td>Intervention</td><td>intravitreal ranibizumab 2.0mg monthly/ PRN</td></tr>
<tr><td>Comparator</td><td>Intravitreal ranibizumab 0.5mg monthly/ PRN</td></tr>
<tr><td>Outcomes</td><td>Primary outcome:
Change in best-corrected visual acuity
Secondary outcome:</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.</td></tr>
<tr><td></td><td>Proportoin of people with a loss of BCVA less than 15 letters from baseline at 12 months (responders)
Proportion of patients with a loss or a gian of BCVA less than 15 letters from basedlin at 12 months (stabilizers)
Proportion of people with 15 letters loss or more BCVA from baseline at 12 months (losers)
Proportion of drpouts befire the final 12 months assessment
Proportion of switcher after the third injection
Adverse event</td></tr>
<tr><td>Analyses</td><td>Both parametric (analysis of variance (ANOVA), paired t-tests) and nonparametric statistics (w2-analysis, Mann–Whitney, Wilcoxon signed-rank, and Friedman) were utilized for comparisons.
A standardized scale
(0=none, 1+=mild, 2+=moderate, and 3+=severe) was used to assess ordinal data, that is, cataract, CME and SRF.
A P-value of ≤0.05 was considered significant.</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Result</td><td>Visual acuity
<table>
<tr><td colspan="4">PRN vs monthly injection</td></tr>
<tr><td></td><td>Ranibizumab, 0.5mg PRN (n=7)</td><td>Ranibizumab, 0.5mg monthly (n=6)</td><td>Effect RR (95%CI)</td></tr>
<tr><td>N, % of people had a gain of >5 letters</td><td>6(85.7%)</td><td>3 (50%)</td><td>1.71 (0.73, 4.03)</td></tr>
<tr><td>% of people had a gain of ≥15 letters</td><td>3 (42.8%)</td><td>2(33.3%)</td><td>2.19 (0.31, 5.31)</td></tr>
<tr><td></td><td>Ranibizumab, 2.0mg PRN (n=11)</td><td>Ranibizumab, 2.0mg monthly (n=12)</td><td></td></tr>
<tr><td>N, % of people had a gain of >5 letters</td><td>7 (63.6%)</td><td>5 (41.7%)</td><td>1.53 (0.68 3.42)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.**

% of people had a gain of ≥15 letters	2 (18.2%)	4 (33.3%)	0.55 (0.12, 2.41)
Monthly 2.0mg vs 0.5mg ranibizumab			
	Ranibizumab 2.0mg monthly (n=12)	Raibizumab 0.5monthly (n=6)	
N, % of people had a gain of >5 letters	5 (41.7%)	3 (50%)	0.83 (0.29, 2.37)
% of people had a gain of ≥15 letters	4 (33.3%)	2(33.3%)	1.00 (0.25, 4.00)
PRN 2.0mg vs 0.5mg ranibizumab			
	Raibizumab 2.0mg PRN (n=11)	Ranibizumab 0.5mg PRN (n=7)	
N, % of people had a gain of >5 letters	7 (63.6%)	6(85.7%)	0.74 (0.43, 1.27)
% of people had a gain of ≥15 letters	2 (18.2%)	3 (42.8%)	0.42 (0.09, 1.94)

Visual acuity at baseline and Month 12

	Ranibizumab 2.0mg (n=23)	Ranibizumab 0.5mg (n=13)	Effect, MD (95%CI)
Baslineline	0.52 (0.15)	0.64 (0.21)	-0.12 (-0.25, 0.01)
Month 12	0.41 (0.29)	0.53 (0.44)	-0.12 (-0.39, 0.15)

Missing data handling/loss to follow up	No loss to follow-up
Was allocation adequately concealed?	Open label study

Bibliographic reference	Chan Ck ; Abraham P ; Sarraf D ; Nuthi As ; Lin Sg ; McCannel Ca. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye 28, 80-87. 2015.
Was knowledge of the allocated intervention adequately prevented during the study?	Open label study
Was the allocation sequence adequately generated?	Unclear
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	N/A
Are reports of the study free of suggestion of selective outcome reporting?	Partially (the results were not reported all by 4 different regimen)

Treat and extend vs routinely month injection

Bibliographic reference	**TREX-AMD 2015** Wykoff CC, Croft DE, Brown DM, Wang R, Payne JF, Clark L, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. Ophthalmology 2015;122(12):2514-22.
Methods	**Number randomized (total and per group):** 60 total participants; 40 to TREX group and 20 to monthly group **Exclusions after randomization**: none reported **Number analyzed (total and per group):** 57 total participants; 37 in the TREX group and 20 in the monthly group **Unit of analysis:** individual (one study eye per participant) **Losses to follow up**: 3 participants (all in the in the TREX group; due to temporal arteritis, lung cancer, or meningitis) **Intention to treat analysis:** no, 3 participants not included in analysis

<table>
<tr><td></td><td>Power calculation: yes, “we calculated an a priori power of 42% to detect noninferiority (significance 5%, one-sided). TREX-AMD 1 year post-hoc analysis demonstrated a power of 88%”
Study design comment: “randomized 1:2, utilizing a noninferiority limit of 5 ETDRS letters and the 12.5 ETDRS letter standard deviation reported in the LUCAS trial”</td></tr>
<tr><td>Participants</td><td>Country: USA (2 centers)
Mean age: 77 years (range 59-96 years)
Gender (percent): 38 (63%) women and 22 (37%) men
Inclusion criteria: “treatment-naïve choroidal neovascularization secondary to exudative AMD with Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) between 78 and 18 (Snellen equivalent, 20/32, 20/500) determined by protocol trial lens refraction, and total area of subretinal hemorrhage and fibrosis comprising less than 50% of the total lesion.”
Exclusion criteria: not reported
Equivalence of baseline characteristics: can’t tell; baseline by group not reported
Diagnoses in participants: choroidal neovascularization secondary to exudative AMD</td></tr>
<tr><td>Interventions</td><td>Intervention 1: intravitreal injection of 0.05-ml ranibizumab (0.5 mg), monthly for first 3 months, then treat-an-extend protocol (“interval between treatments was tailored based on exudative disease activity: eyes were treated at each visit, no more frequently than every 4 weeks and no less frequently than every 12 weeks”)
Intervention 2: intravitreal injection of 0.05-ml ranibizumab (0.5 mg), monthly for one year

<table>
<tr><th></th><th>Intervention1</th><th>Intervention2</th></tr>
<tr><td>Agent</td><td>Ranibizumab</td><td>ranibiumab</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>0.5mg</td></tr>
<tr><td>Frequency</td><td>Monthly for 3 months, then treat-and-extend protocol</td><td>Monthly for one year</td></tr>
</table>

Follow-up: 1 year reported, 2 years planned
Frequency of assessments for retreatment: every 1-4 weeks, based on exudative disease activity in the TREX group</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: ETDRS BCVA change from baseline</td></tr>
</table>

Secondary outcomes, as defined: "mean change in CRT by SD OCT, total number of intravitreal injections, percentage of patients with persistent exudative disease activity by SD OCT, percentage of patients gaining or losing 10 or 15 ETDRS letters at month 12, and the incidence and severity of ocular and systemic adverse events"
Adverse events (Y/N): yes
Intervals at which outcome assessed: every month for 12 months

Results

Visual acuity (12 months)

	Ranibizumab (n=40)	Ranibiumab (n=20)	RR/MD (95%CI)
Dose	0.5mg	0.5mg	
Frequency	Monthly for 3 months, then treat-an-extend protocol	Monthly for one year	
Gain of ≥15 letters, n(%)	10 (25)	3 (15)	1.67 (0.52, 5.39)
Mean BCVA, (SD)	72.1 (17.08)	69.4 (10.73)	2.70 (-4.38, 9.78)

Adverse event (12 months)

	Ranibizumab (n=40)	Ranibiumab (n=20)	RR (95%CI)
Dose	0.5mg	0.5mg	
Frequency	Monthly for 3 months, then treat-an-extend protocol	Monthly for one year	
Ocular adverse event, n(%)	10	2	2.50 (0.60, 10.34)
Systematic adverse event	5	0	5.63 (0.33, 97.10)

Number of injections (12 months)

Agent	Ranibizumab (n=40)	Ranibizumab (n=20)
Dose	0.5mg	0.5mg
Frequency	Monthly for 3 months, then treat-an-extend protocol	Monthly for one year

	Mean number of injections	10.1	13.0
Notes	**Full study name:** The Treat-and-Extend Protocol in Patients with Wet Age-Related Macular Degeneration **Type of study**: published **Trial registration (Y/N):** NCT01748292 **Funding sources**: "Supported by Genentech, Inc., South San Francisco, California. The funding organization had no role in the design or conduct of this research." **Declarations of interest**: "The author(s) have no proprietary or commercial interest in any materials discussed in this article: C.C.W.: Research support – Alcon, Allergan, Genentech, Regeneron; Consultant – Alcon, Allergan, Bayer, Genentech, Regeneron; Lecturer – Allergan, Genentech, Regeneron. D.M.B.: Research support – Alcon, Allergan, Genentech, Regeneron; Consultant – Alcon, Allergan, Bayer, Genentech, Regeneron; Lecturer – Bayer, Roche. L.C.: Research support – Genentech; Consultant – Regeneron; Lecturer – Regeneron, Genentech, Bayer; Travel – Bayer, Regeneron, Genentech. J.F.P.: Research support – Genentech. S.S.: Research support – Genentech, Carl Zeiss Meditec, Optos, Allergan; Personal fees – Genentech, Carl Zeiss Meditec, Optos, Allergan, Roche, Novartis, Alcon, Iconic." **Study period**: February 2013 to January 2014 **Reported subgroup analyses (Y/N):** none reported		

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported. "The Treat-and-Extend Protocol in Patients with Wet Age-Related Macular Degeneration (TREX-AMD) is a phase III , multicenter, randomized, controlled clinical trial."
Allocation concealment (selection bias)	Low risk	"At enrollment, patients were randomized sequentially by a blinded study coordinator to the monthly or TREX cohort"
Masking of participants (performance bias)	Unclear risk	Not reported

Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	3 of 60 (5%) participants were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Trial planned for 2 years; results at 1 year reported (study ongoing).
Other bias	Unclear risk	Funded by manufacturer of the intervention.

PRN

Without vs with loading phase

Bibliographic reference	**Barikian 2015** Barikian A, Mahfoud Z, Abdulaal M, Safar A, Bashshur ZF. Induction with intravitreal bevacizumab every two weeks in the management of neovascular age-related macular degeneration. American Journal of Ophthalmology 2014;159(1):131-7.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group):** 90 total participants; 30 participants in each of 3 groups **Exclusions after randomization**: none reported **Number analyzed (total and per group):** 90 participants; 30 participants in each of 3 groups **Unit of analysis**: individual (one study eye per participant) **Losses to follow-up**: none reported **Intention to treat analysis**: all participants randomized were analysed **Power calculation**: none reported **Study design comment**: none
Participants	**Country:** Lebanon **Mean age**: 77 years **Gender (percent)**: 41 (46%) women and 49 (54%) men **Inclusion criteria**: "All participants had to be older than 50 years with subfoveal choroidal neovascular membrane (CNV) attributable to AMD diagnosed by fluorescein angi- ography. Patients were required to have best-corrected visual

<table>
<tr><td></td><td>acuity (BCVA) of 50 letters or better (20/100 Snellen equivalent or better) using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Additionally, presence of subretinal fluid, cystic maculopathy, or central retinal thickness >250 mm had to be documented on optical coher- ence tomography (OCT) with CNV less than 5400 mm in greatest linear dimension. All patients had to understand and sign the study consent form."
Exclusion criteria: "prior treatment for CNV; submacular hemorrhage or scarring involving the fovea; corneal, lenticular, or vitreous opacification that prevents good-quality angiograms or OCT; history of uveitis; history of vitrectomy; proliferative diabetic retinopathy; and other ocular conditions that affect vision. Patients with cardiovascular, cerebrovascular, or peripheral vascular event less than 6 months prior to enrollment were also excluded. All CNV lesion types were included except for retinal angiomatous proliferation and polypoidal choroidal vasculopathy, since they may respond differently to treatment.
Equivalence of baseline characteristics: “there were significantly more female patients recruited to the monthly induction arm as compared to the biweekly induction arm”</td></tr>
<tr><td>Interventions</td><td>Intervention: intravitreal 1.25 mg bevacizumab injection (Avastin; Roche, Basel, Switzerland)
Treatment schedule 1: first injection, then PRN
Treatment schedule 2: every 2 weeks for first 3 injections, then PRN
Treatment schedule 3: every 4 weeks for first 3 injections, then PRN
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention 3</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25</td><td>1.25</td></tr>
<tr><td>Frequency</td><td>One injection, the PRN</td><td>Every 2 weeks for 3 injections then PRN</td><td>Every 4 weeks for 3 injections, then PRN</td></tr>
</table>

Follow-up: 12 months
Frequency of assessments for retreatment: monthly</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: mean initial fluid-free interval after induction period
Secondary outcomes, as defined: mean improvement in BCVA (ETDRS charts at 4 meters) and central retinal thickness
Adverse events: ocular and systemic adverse events
Review outcomes not reported: gain of 15 letters visual acuity, quality of life, number of injections, cost
Intervals at which outcome assessed: every month for 12 months</td></tr>
</table>

Results

Visual acuity (12 months)

	Bevacizumab (n=30)	Bevacizumab (n=30)	Bevacizumab (n=30)
Dose	1.25mg	1.25	1.25
Frequency	One injection, the PRN	Every 2 weeks for 3 injections then PRN	Every 4 weeks for 3 injections, then PRN
Gain of ≥ 15 letters, no.	10	6	12
Loss of ≥ 15 letters, no.	0	0	0

Number of injections (12 months)

	Intervention 1	**Intervention 2**	**Intervention 3**
Agent	Bevacizumab	Bevacizumab	Bevacizumab
Dose	1.25mg	1.25	1.25
Mean number of injections	6.07	6.47	6.27

Notes

Full study name: not reported
Trial registration: not reported
Funding sources: American University of Beirut Medical Center, Beirut, Lebanon
Declarations of interest: "The authors indicate no financial interest in any product discussed in this study. Z.F.B. has participated on advisory boards for Novartis and Bayer; has received honoraria from Bayer (Leverkusen, Germany) and Novartis (Basel, Switzerland) as invited speaker; and has received research grants from Novartis and Allergan (Center Valley, Pennsylvania, USA)."
Study period: September 2010 to 2012
Subgroup analyses: none reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported: "Patients were randomized in a 1:1:1 ratio to 1 of 3 groups based on the induction sequence."

Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	No missing data reported
Selective reporting (reporting bias)	Unclear risk	Trial protocol and trial registry were not reported.
Other bias	Low risk	None identified

Bibliographic reference	**BeMOc 2013** Menon G, Chandran M, Sivaprasad S, Chavan R, Narendran N, Yang Y. Is it necessary to use three mandatory loading doses when commencing therapy for neovascular age-related macular degeneration using bevacizumab? (BeMOc Trial). Eye (Basingstoke) 2013;27(8):959-63.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group):** 100 total participants; 49 participants in no loading group, 50 participants in loading group (unclear which group 1 participant was in) **Exclusions after randomization**: 1 participant (unclear which group) **Number analyzed (total and per group):** 99 participants; 49 participants in no loading group; 50 participants in loading group **Unit of analysis**: individual (one study eye per participant) **Losses to follow up**: none reported **Intention to treat analysis:** participants analyzed as they are randomized, 1 participant excluded from analysis **Power calculation**: none reported; "a reasonable and pragmatic sample size of 100 patients was selected to enable the study to be carried out as a monocentric study" **Study design comment**: none

Participants	**Country**: UK **Mean age**: not reported; 13 participants ages 61 to 70; 35 participants ages 71 to 80; 51 participants ages 81+ **Gender (percent):** 72 (73%) women and 27 (27%) men **Inclusion criteria**: “Eligible criteria included treatment-naive patients with active subfoveal choroidal neovascularisation of minimally classic or occult type, secondary to age-related macular degeneration, confirmed on fluorescein angiography, and no other visually significant ocular pathology." **Exclusion criteria:** “1. Medical conditions: 1.1. Uncontrolled hypertension 1.2. Patients on more than 3 antihypertensive medications 1.3. Patients in whom a change in anti-hypertensive drug was initiated within 3 months preceding baseline visit. 1.4. Previous thrombembolic phenomenon 1.5. On Warfarin or anticoagulants 1.6. Recent Myocardial Infarction (MI) 1.7. Recent major surgery (within 28 days) 2. Ocular conditions: 2.1. Glaucoma (IntraOcular Pressure [IOP] >25, on anti-glaucoma treatment, glaucoma surgery) 2.2. Active intraocular or extraocular inflammation 2.3. Retinal vascular disease 2.4. Other sources of chorodal neovascular membrane 2.5. Previous PhotoDynamic Therapy (PDT) 2.6. Predominantly classic membranes 2.7. Previous cataract surgery (within 6 months) 2.8. Aphakia 2.9. Other retinal conditions that may effect visual outcome 3. Other: 3.1. Allergy to Fluorescein 3.2. Inability to obtain colour photographs, fluorescein angiogram, Optical Coherence Tomography (OCT) images 3.3. Allergy to anti Vascular Endothelial Growth Factor (VEGF) medications 3.4. Allergy to humanised monoclonal antibody

<table>
<tr><td></td><td>3.5. Inability to comply with follow-up procedures” from trial registry”
Equivalence of baseline characteristics: “The two groups were balanced at baseline in terms of mean visual acuities and mean CMT.”</td></tr>
<tr><td>Interventions</td><td>Intervention: intravitreal 1.25 mg bevacizumab injection (Avastin; Roche, Basel, Switzerland)
Treatment schedule 1: PRN (no loading)
Treatment schedule 2: every 4 weeks for first 3 injections, then PRN (loading)
<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><td>Agent</td><td>Bevacizumab</td><td>Bevacizumab</td></tr>
<tr><td>Dose</td><td>1.25mg</td><td>1.25mg</td></tr>
<tr><td>Frequency</td><td>PRN (no loading)</td><td>every 4 weeks) for first 3 injections, then PRN</td></tr>
</table>
Follow-up: 54 weeks
Frequency of assessments for retreatment: every 6 weeks</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: proportion with visual stability, defined as less than or equal to loss of 15 letters from baseline
Secondary outcomes, as defined: central macular thickness (CMT) on OCT
Adverse events: ocular and systemic adverse events
Review outcomes not reported: number of injections, cost
Intervals at which outcome assessed: every 6 weeks for 54 weeks</td></tr>
</table>

Results

Visual acuity (54 weeks)

	Bevacizumab (n=49)	Bevacizumab (n=50)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	PRN (no loading)	every 4 weeks) for first 3 injections, then PRN	
Loss of <15 letters, n(%)	33 (67)	42 (84)	0.80 (0.64, 1.01)
Gain of ≥ 10 letters	13 (26.3)	14 (28.0)	0.95 (0.50, 1.80)

Adverse events (54 weeks)

	Bevacizumab (n=49)	Bevacizumab (n=50)	RR (95%CI)
Dose	1.25mg	1.25mg	
Frequency	PRN (no loading)	every 4 weeks) for first 3 injections, then PRN	
Conjunctivitis	1 (2)	2 (4)	0.51 (0.05, 5.45)
Subconjunctival haemorrhage	0	1	

Number of injections (54 weeks)

Agent	Bevacizumab	Bevacizumab
Dose	1.25mg	1.25mg
Frequency	PRN (no loading)	every 4 weeks) for first 3 injections, then PRN
Mean number of injections	4.7	5.8

Notes

Full study name: not reported
Trial registration: EUDRACT No: 2006-003033-33, ISRCTN number: 12980412
Funding sources: Frimley Park Hospital NHS Trust (UK)
Declarations of interest: "The authors declare no conflict of interest."
Study period: November 2006 to November 2008
Subgroup analyses: none reported

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	1 (1%) of 100 participants excluded.
Selective reporting (reporting bias)	Unclear risk	Study protocol could not be retrieved from EUDRACT. Primary and secondary outcomes not reported in trial registry.
Other bias	Low risk	None identified

4 weeks vs 12 weeks interval loading phase

Bibliographic reference	**CLEAR-IT2 2011** Heier JS, Boyer D, Nguyen QD, Marcus D, Roth DB, Yancopoulos G, et al. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. Ophthalmology 2011;118(6):1098-106.
Methods	**Study design**: parallel-group randomized controlled trial **Number randomized (total and per group)**: 159 total participants; 32 participants in 0.5 mg q4 wks group; 32 participants in 2 mg q4 wks group; 32 participants in 0.5 mg q12 wks group; 32 participants in 2 mg q12 wks group; 31 participants in 4 mg q12 wks group;

	Exclusions after randomization: none reported **Number analyzed (total and per group**): 159 participants in total; 32 participants in 0.5 mg q4 wks group; 32 participants in 2 mg q4 wks group; 32 participants in 0.5 mg q12 wks group; 32 participants in 2 mg q12 wks group; 31 participants in 4 mg q12 wks group **Unit of analysis:** individual (one study eye per participant) **Losses to follow up**: none reported **Compliance**: not reported **Intention to treat analysis:** all participants analysed as randomised **Reported power calculation**: not reported **Study design comment:** none
Participants	**Country**: USA **Mean age (SD):** 78.2 (not reported) years in total; by group not reported **Gender (percent):** 38 men and 62 women in total; by group not reported **Inclusion criteria**: "Patients eligible for the study were ?50 years old, had a diagnosis of subfoveal CNV secondary to wet AMD, and met the following inclusion criteria: CR/LT ?300 um, Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA letter score of 73 to 34 letters (20/40 –20/200), loss of ≥5 ETDRS letters in BCV A over the preceding 6 months for previously treated patients with minimally classic or occult lesions, linear diameter of lesion 5400 µm by fluorescein angiography, subretinal hemorrhage (if present) sparing the fovea and comprising ≤50% of total lesion, area of scar ≤25% of total lesion, and sufficient clarity of ocular media to allow retinal photography." Exclusion criteria: "Exclusion criteria were vitreous hemorrhage in preceding 4 weeks; aphakia or pseudophakia with absence of a posterior capsule (unless as a result of a yttrium aluminum garnet capsulotomy); significant subfoveal atrophy or scarring; active ocular inflamma- tion; corneal transplant; previous uveitis in either eye; or history of macular hole of grade 3 or higher. Patients who had previously received any of the following treatments in the study eye were excluded: Subfoveal thermal laser therapy, any operative intervention for AMD, extrafoveal laser coagulation treatment or photodynamic therapy in preceding 12 weeks, pegaptanib sodium in preceding 8 weeks, systemic or intravitreal treatment with VEGF Trap-Eye, ranibizumab, or bevacizumab at any time, juxtascleral steroids, anecortave acetate, or intravitreal triamcinolone acetonide or other steroids in preceding 24 weeks. Additional reasons for exclusion were

<table>
<tr><td></td><td>other causes of CNV in either eye; active ocular infection; congenital lid anomalies that might interfere with intravitreal administration; any retinal disease other than CNV in either eye; previous trabeculectomy or pars plana vitrectomy; cup-to-disc ratio ?0.8, intraocular pressure ≥25 or receipt of >2 agents for treatment of glaucoma; allergy to povidone iodine, fluorescein, or recombinant proteins; absolute neutrophil count 1000 cells/mm3; human immunodeficiency virus positivity, active systemic infection requiring antibiotics; proteinuria >1+ or urine protein:creati- nine ratio ≥1 on 2 repeated determinations within 1 week; New York Heart Association class III or IV; symptomatic cardiovascular or peripheral vascular disease, malignancy other than basal cell carcinoma in preceding 2 years; and any other conditions or laboratory abnormalities that could interfere with disease assessment or patient participation in the study. The use of standard agents or other anti-VEGF agents was not permitted before week 16.”
Equivalence of baseline characteristics: can’t tell; baseline by group not reported
Diagnoses in participants: subfoveal choroidal neovascularization secondary to wet age-related macular degeneration</td></tr>
<tr><td>Interventions</td><td>Intervention 1: intravitreal injection of VEGF Trap-Eye 0.5 mg every 4 weeks (0.5 mg q4 wks)
Intervention 2: intravitreal injection of VEGF Trap-Eye 2 mg every 4 weeks (2 mg q4 wks)
Intervention 3: intravitreal injection of VEGF Trap-Eye 0.5 mg every 12 weeks (0.5 mg q12 wks)
Intervention 4: intravitreal injection of VEGF Trap-Eye 2 mg every 12 weeks (2 mg q12 wks)
Intervention 5: intravitreal injection of VEGF Trap-Eye 4 mg every 12 weeks (4 mg q12 wks)

<table>
<tr><th></th><th>Intervention 1</th><th>Intervention 2</th><th>Intervention 3</th><th>Intervention 4</th><th>Intervention 5</th></tr>
<tr><td>Agent</td><td>Aflibercept</td><td>Aflibercept</td><td>Aflibercept</td><td>Aflibercept</td><td>Aflibercept</td></tr>
<tr><td>Dose</td><td>0.5mg</td><td>2mg</td><td>0.5mg</td><td>2mg</td><td>4 mg</td></tr>
<tr><td>Frequency</td><td>Every 4 weeks</td><td>every 4 weeks</td><td>every 12 weeks</td><td>every 12 weeks</td><td>every 12weeks</td></tr>
</table>

Follow-up: 20 weeks and 1 year
Frequency Criteria of assessments for retreatment: “An increase in CR/LT ?100 ?m as measured by OCT; a loss of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; persistent fluid as indicated by OCT; new-onset classic neovascularization; new or persistent leak on FA; or new macular hemorrhage.”</td></tr>
<tr><td>Outcomes</td><td>Primary outcome, as defined: change from baseline in central retinal/lesion thick ness (CR/LT) at week 12</td></tr>
</table>

Secondary outcomes, as defined: change in best-corrected visual acuity (BCVA), proportion of patients with a gain of ≥15 letters, proportion of patients with a loss of ≥15 letters, and safety
Adverse events (Y)
Intervals at which outcome assessed: every 4 weeks for 20 weeks

Results

Visual acuity (52 weeks)

Agent	Aflibercept (n=32)	Aflibercept (n=31)	Aflibercept (n=32)	Aflibercept (n=31)	Aflibercept (n=31)
Dose	0.5mg	2mg	0.5mg	2mg	4 mg
Frequency	Every 4 weeks	every 4 weeks	every 12 weeks	every 12 weeks	every 12weeks
Gain of ≥15 letters, n (%)	6 (19)	9 (29)	7 (22)	9 (29)	3(10)
Loss <15 letters	28(88)	31 (100)	28 (88)	28 (90)	30 (97)
Mean change in BCVA, letters	5.4 (12.34)	9.0 (8.50)	2.6 (10.91)	5.2 (9.81)	4.2 (6.63)

Adverse event
Number of adverse events were reported in a total group.

Number of injections ((52 weeks)

Agent	Aflibercept	Aflibercept	Aflibercept	Aflibercept	Aflibercept
Dose	0.5mg	2mg	0.5mg	2mg	4 mg
Frequency	Every 4 weeks	every 4 weeks	every 12 weeks	every 12 weeks	every 12weeks
Mean no. of injections (12-52 weeks)	2.52	1.55	1.84	2.48	1.7

Notes	**Full study name**: Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial [CLEAR-IT 2]) **Type of study:** published or unpublished **Trial registration:** NCT00320788 **Funding sources:** Regeneron Pharmaceuticals, Inc. and Bayer HealthCare AG **Declarations of interest:** "David M. Brown – Alcon Laboratories – Consultant, Grant/Financial Support; Alimera – Grant/Financial Support; Allergan – Consultant, Grant/ Financial Support; Carl Zeiss Meditec – Consultant; CoMentis – Grant/ Financial Support; Eyemaginations – Consultant; Genentech – Consultant, Grant/Financial Support, Lecturer; Heidelberg Engineering – Consultant, Lecturer; Jerini Ophthalmics – Consultant, Grant/Financial Support, Lec- turer; NeoVista – Consultant, Grant/Financial Support, Lecturer; Neuro- tech – Grant/Financial Support; Novartis Pharmaceuticals – Consultant, Grant/Financial Support; Oraya Therapeutics – Consultant; Othera – Grant/ Financial Support; Oxigene – Grant/Financial Support; Pfizer Ophthalmics – Consultant, Grant/Financial Support; Regeneron – Consultant, Grant/ Financial Support, Lecturer; Steba – Consultant. Jeffrey S. Heier: Acucela – Consultant; Alcon Laboratories – Consultant, Grant/Financial Support; Allergan – Consultant, Grant/Financial Support; Bausch & Lomb – Consultant; CoMentis – Grant/Financial Support; Eyemaginations – Consultant; Fovea – Consultant; Genentech – Consul- tant, Grant/Financial Support, Lecturer; Genzyme – Consultant; Heidel- berg Engineering – Consultant, Lecturer; iScience – Consultant, Grant/ Financial Support; Ista Pharmaceuticals – Consultant, Grant/Financial Support; Jerini Ophthalmics – Consultant, Grant/Financial Support, Lecturer; LPath – Consultant; NeoVista – Consultant, Grant/Financial Support, Lecturer; Neurotech – Grant/Financial Support; Notal Vision – Consultant; Novartis Pharmaceuticals – Consultant, Grant/Financial Support; Optherion – Consultant; Optimedica – Royalties; Oraya Therapeutics – Consul- tant; Oxigene – Grant/Financial Support; Paloma – Consultant, Grant/ Financial Support; Pfizer Ophthalmics – Consultant, Grant/Financial Support; Regeneron – Consultant, Grant/Financial Support, Lecturer; Resolvyx Pharmaceuticals – Consultant; Schering Plough Research Institute – Consultant; Scyfix – Consultant; Steba – Consultant; VisionCare Ophthal- mic Technologies – Consultant, Grant/Financial Support. Thomas Ciulla: Neovista – Consultant; Regeneron – Consultant; Pfizer – Consultant; Genentech – Grant/Financial Support; Regeneron – Grant/ Financial Support; Allergan – Grant/Financial Support; Alimera – Grant/ Financial Support; Othera – Grant/Financial Support; Glaxo-Smith-Kline – Grant/Financial Support; Optko – Grant/Financial Support; National Eye Institute/National Institutes of Health – Grant/Financial Support. Prema Abraham: Genentech – Consultant, Grant/Financial Support; Alcon – Consultant, Grant/Financial Support; Novartis – Consultant, Grant/Finan- cial Support; Regeneron – Grant/Financial Support; Allergan – Grant/ Financial Support; Opko Health – Grant/Financial Support; Jerini Ophthal- mic – Grant/Financial Support; Pfizer – Grant/Financial Support; Eli Lilly – Grant/Financial Support; Alimera –

	Grant/Financial Support; VRT – Grant/Financial Support; Schering-Plough – Grant/Financial Support. George Yancopoulous, Neil Stahl, Avner Ingerman, Robert Vitti, Alyson J. Berliner, Ke Yang: Regeneron – Employee at the time the study was conducted. Quan Dong Nguyen: Bausch & Lomb – Consultant; Genentech – Grant/ Financial Support; Regeneron – Grant/Financial Support. Supported by Regeneron Pharmaceuticals, Inc. and Bayer HealthCare AG. The sponsors participated in the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, and the preparation, review, and approval of the manuscript. ” **Study period**: May 2006 and April 2007 **Reported subgroup analyses:** none reported

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported. “The CLEAR-IT 2 was a prospective, double-masked, random- ized study conducted at 33 sites in the United States.”
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Low risk	“Examiners were masked to treatment assignment and performed no other study assessments. “ “Stratus (software version 4.0 or higher) optical coherence tomography scans (Carl Zeiss Med- itec, Inc., Dublin, CA) read at a masked independent central reading center (Digital Optical Coherence Tomography Reading Center [DOCTR], Cleveland, OH).”
Incomplete outcome data (attrition bias)	Low risk	5 or 159 (3.2%) participants were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes in trial registry was reported in the full-text.
Other bias	Low risk	Funded by manufacturer of the intervention.

Wait & extend vs Treat & observe

The Eldem study described below was identified by update searches undertaken after the search date of the Cochrane systematic reviews used above.

Bibliographic reference	Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.
Country/ies	Turkey
Study type	RCT
Aim of the study	To compare visual outcomes, number of visits and ranibizumab injections in patients treated with a Wait & Extend (W&E) or Treat & Observe (T&O) regimen.
Study dates	2010-2012
Sources of funding	Not reported
Sample size	93 ranodmised
Inclusion Criteria	The study enrolled patients aged 50 years or over with primary or recurrent subfoveal CNV secondary to AMD, regardless of the lesion type, who had not previously received anti-VEGF treatment for AMD. Inclusion criteria further required patients to have a CNV area ≥50% of the total lesion size; in patients with occult lesions with minimal or no classic component, the total lesion area had to be ≤12 disc areas, and in patients with predominantly classic lesions, the greatest linear dimension had to be ≤9 disc areas. Patients were required to have a best corrected visual acuity (BCVA) score between 73 and 34 letters (approximately 20/40 to 20/200 Snellen equivalent). Where both eyes were eligible, the eye with better VA was chosen for treatment unless the investigator deemed, based on medical justification, that the other eye was a more appropriate candidate for the study.
Exclusion Criteria	Key exclusion criteria included previous treatment for AMD in the study eye except juxtafoveal or extrafoveal laser photocoagulation administered at least 1 month before the study; previous participation in a clinical trial or treatment with investigational drugs within the 30 days before screening; Previous treatment with verteporfin, external beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy or transpupillary thermotherapy before the study; previous or current intravitreal or sub-Tenon's agent to the study eye; previous submacular surgery or any other surgical intervention.

<table>
<tr><th>Bibliographic reference</th><td>Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.</td></tr>
<tr><td></td><td>Also excluded were patients with CNV in either eye due to other causes; subfoveal fibrosis or atrophy in the study eye; a tear in the retinal pigment epithelium of the study eye involving the macula; vitreous haemorrhage or rhegmatogenous retinal detachment or macular hole in the study eye;
presence of subretinal haemorrhage affecting the fovea centralis or if the size of the haemorrhage was ≥50% of the total lesion area or ≥1 disc area; any ocular condition that may require medical or surgical management for treatment or which, if left untreated, may result in loss of at least two lines of BCVA.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Wait & extend (n=48)</th><th>Treat & observe (n=45)</th></tr>
<tr><td>Median age (rang)</td><td>70.4 (53.6, 86.8)</td><td>70.3 (52.7-83.8)</td></tr>
<tr><td>Male: n (%)</td><td>25 (52%)</td><td>25 (56%)</td></tr>
<tr><td>Caucasuan: n(%)</td><td>48 (100)</td><td>45 (100)</td></tr>
<tr><td>Mean BCVA (SD)</td><td>60 (13)</td><td>60 (14)</td></tr>
</table>
</td></tr>
<tr><td>Study visits and procedures</td><td>All enrolled patients received three monthly loading doses of 0.5 mg ranibizumab (Lucentis;Novartis Pharma AG, Basel, Switzerland, and Genentech Inc., South San Francisco, CA, USA) via intravitreal injection administered according to the locally approved summary of product characteristics.
After the loading-dose period, patients were randomized (1:1) according to a blocked randomization list, which was produced by Novartis using a validated system.
Upon enrolment, patients received the lowest available randomization number, which allocated them to one of two treatment arms. In the T&O arm, after the three loading doses, patients were invited for monthly visits and were re-treated if the lesion was active. In the W&E arm, after the three loading doses, patients were invited to return for a follow-up visit 1 month after the last visit. For patients with no active lesions at this visit, treatment was not administered and the interval to the next visit was extended by 2 weeks to a maximum of 8 weeks between visits. Patients whose lesions became active at any of these visits were re-treated and the follow-up schedule started over.
For both groups, patients were treated according to the criteria of the Royal College of Ophthalmology (2008). Disease activity was classified as retinal, subretinal or subretinal pigment epithelium fluid or haemorrhage, as determined clinically and/or on optical coherence tomography (OCT), lesion growth on fundus fluorescein angiography (FA) and/or VA loss of >5 letters. No specific criterion values for OCT and FA findings were set and this was left to investigator discretion.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.</th></tr>
<tr><td>Intervention</td><td>intravitreal ranibizumab 1.25mg wait & extent (W &E)</td></tr>
<tr><td>Comparator</td><td>Intravitreal ranibizumab 0.5mg treat & observe (T&O)</td></tr>
<tr><td>Outcomes</td><td>Primary outcome:
change in BCVA from baseline to Month 12 in the two treatment groups (logMAR and letter count).
Secondary outcome:
two treatment regimens in terms of the number of visits and injections received
quality of life of ranibizumab-treated patients as measured by Visual Function Questionnaire (VFQ-25)
any differences in ocular and non-ocular adverse events (AEs) and serious adverse events (SAEs)</td></tr>
<tr><td>Analyses</td><td>Descriptive statistics were used to summarize patient demographics and baseline data based on the safety population, which consisted of all patients who received at least one dose of ranibizumab.
The efficacy analysis was performed in the per protocol population, which consisted of all patients evaluated at baseline and at 12 months (±2 months). The baseline and followup values, and the changes in each group, were compared using a Mann–Whitney U-test. The safety analysis was performed in the safety population with groups compared using cross-table statistics or a Mann–Whitney U-test.
Longitudinal change was evaluated with a Wilcoxon test or McNemar test for variable type. Throughout, significance was set at a level of 0.05. No procedure was defined for missing values. According to the original study protocol, the data were to be analysed using parametric statistical tests; however, analysis revealed that variables showed a non-parametric distribution, and hence non-parametric tests were used in the final analysis.</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Result</td><td>Visual acuity
<table>
<tr><th></th><th>Wait & Extend (n=38)</th><th>Treat & Observe (n=39)</th><th>Effect (MD, RR) (95%CI)</th></tr>
<tr><td>Mean change in VA, letters (SD)</td><td>7.7 (15.9)</td><td>3.2 (20.9)</td><td>4.5 (-3.78, 12.78)</td></tr>
<tr><td>N, % of people had a gain of ≥10 letters</td><td>29 (76%)</td><td>24 (62%)</td><td>1.24 (0.91, 1.68)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.
<table>
<tr><td>N, % of people had a gain of ≥15 letters</td><td>13(34%)</td><td>9(23%)</td><td>1.48 (0.72, 3.05)</td></tr>
<tr><td>% of people had a loss of >15 letters</td><td>4 (10.5%)</td><td>4 (10.3%)</td><td>1.03 (0.28, 3.81)</td></tr>
<tr><td>% of people had a loss of ≥30 letters</td><td>1 (2.6)</td><td>2 (5.1)</td><td>0.51 (0.05, 5.43)</td></tr>
<tr><td>Number of injections (range)</td><td>5.5 (3.0-12.0)</td><td>6.4 (3.0-12.0)</td><td>Cannot be estimated</td></tr>
</table>
Adverse event
<table>
<tr><td></td><td>Wait & Extend (n=38)</td><td>Treat & Observe (n=39)</td><td>Effect (RR) (95%CI)</td></tr>
<tr><td>Any ocular AEs</td><td>24</td><td>25</td><td>0.99 (0.70,1.38)</td></tr>
<tr><td>Any serious AEs</td><td>5</td><td>3</td><td>1.71 (0.44, 6.66)</td></tr>
<tr><td>Discontinued due to SAE</td><td>2</td><td>1</td><td>2.05 (0.19, 21.71)</td></tr>
</table></td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>The efficacy analysis was performed in the per protocol population. 10 people in wait & extend regimen discontinued and 6 people in treat & observe regimen.</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>Open label study</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td>Open label study</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>Partially</td></tr>
</table>

Bibliographic reference	Eldem B M; Muftuoglu G ; Topbas S ; Cakir M ; Kadayifcilar S ; Ozmert E ; Bahcecioglu H ; Sahin F ; Sevgi S ; group Salute study. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Opthalmologica 93 (6) 2015.
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes