



Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial



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Summary

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Background Bevacizumab has been suggested to have similar effectiveness to ranibizumab for treatment of neovascular age-related macular degeneration. The Inhibition of VEGF in Age-related Choroidal Neovascularisation (IVAN) trial was designed to compare these drugs and different regimens. Here, we report the findings at the prespecified 2-year timepoint.

Methods In a multicentre, 2x2 factorial, non-inferiority randomised trial, we enrolled adults aged at least 50 years with active, previously untreated neovascular age-related macular degeneration and a best corrected distance visual acuity (BCVA) of at least 25 letters from 23 hospitals in the UK. Participants were randomly assigned (1:1:1:1) to intravitreal injections of ranibizumab (0.5 mg) or bevacizumab (1.25 mg) in continuous (every month) or discontinuous (as needed) regimens, with monthly review. Study participants and clinical assessors were masked to drug allocation. Allocation to continuous or discontinuous treatment was masked up to 3 months, at which point investigators and participants were unmasked. The primary outcome was BCVA at 2 years, with a prespecified non-inferiority limit of 3.5 letters. The primary safety outcome was arterial thrombotic event or hospital admission for heart failure. Analyses were by modified intention to treat. This trial is registered, number ISRCTN92166560.

Findings Between March 27, 2008, and Oct 15, 2010, 628 patients underwent randomisation. 18 were withdrawn; 610 received study drugs (314 ranibizumab; 296 bevacizumab) and were included in analyses. 525 participants reached the visit at 2 years: 134 ranibizumab in continuous regimen, 137 ranibizumab in discontinuous regimen, 127 bevacizumab in continuous regimen, and 127 bevacizumab in discontinuous regimen. For BCVA, bevacizumab was neither non-inferior nor inferior to ranibizumab (mean difference -1.37 letters, 95% CI -3.75 to 1.01 ; $p=0.26$). Discontinuous treatment was neither non-inferior nor inferior to continuous treatment (-1.63 letters, -4.01 to 0.75 ; $p=0.18$). Frequency of arterial thrombotic events or hospital admission for heart failure did not differ between groups given ranibizumab (20 [6%] of 314 participants) and bevacizumab (12 [4%] of 296; odds ratio [OR] 1.69, 95% CI 0.80–3.57; $p=0.16$), or those given continuous (12 [4%] of 308) and discontinuous treatment (20 [7%] of 302; 0.56, 0.27–1.19; $p=0.13$). Mortality was lower with continuous than discontinuous treatment (OR 0.47, 95% CI 0.22–1.03; $p=0.05$), but did not differ by drug group (0.96, 0.46–2.02; $p=0.91$).

Interpretation Ranibizumab and bevacizumab have similar efficacy. Reduction in the frequency of retreatment resulted in a small loss of efficacy irrespective of drug. Safety was worse when treatment was administered discontinuously. These findings highlight that the choice of anti-VEGF treatment strategy is less straightforward than previously thought.

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Introduction

Neovascular age-related macular degeneration is a common bilateral condition that affects people aged 50 years and older, and causes severe impairment of central vision. Intravitreal treatment with ranibizumab, an antibody to vascular endothelial growth factor (VEGF), was shown to be effective in neovascular age-related macular degeneration compared with photodynamic therapy or no treatment.^{1,2} Anti-VEGF drugs were thus established as a standard of care for neovascular age-related macular degeneration.^{3–6}

Bevacizumab, an antibody to VEGF that is licensed for treatment of bowel cancers, is the parent molecule from which ranibizumab was developed. Small non-randomised

studies^{7–9} done while ranibizumab was awaiting marketing authorisation suggested that bevacizumab had similar effectiveness to ranibizumab for treatment of neovascular age-related macular degeneration. These findings were important, because every dose of ranibizumab is expensive and treatment can be needed every month for several years.^{3–6} The dose at which bevacizumab is supplied is sufficiently large to allow aliquoting into many smaller fractions for intraocular administration, thus offering large cost savings. Its use off licence, given in a similar way to ranibizumab, has spread rapidly across the world.

The absence of robust information about the safety of bevacizumab in the treatment of neovascular age-related macular degeneration and uncertainty about treatment

frequency for both bevacizumab and ranibizumab led us to undertake the Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial in the UK.⁴ The Comparison of Age-related macular degeneration Treatments Trials (CATT) were developed in parallel in the USA.^{3,5}

We reported an interim analysis after 1 year of follow-up in 2012, and a pooled analysis of the IVAN and CATT 1-year data.⁴ These analyses showed that functional outcomes were similar between the two drugs and between monthly (continuous) and intermittent treatment administration (as needed or discontinuous) but that the risk of a systematic serious adverse event (SAE) was higher with bevacizumab than ranibizumab. Here, we report the definitive findings of the IVAN trial at the prespecified primary 2-year timepoint and meta-analyses pooling key outcomes from both trials after 2 years.

Methods

Study design and participants

We undertook a multicentre, 2x2 factorial, non-inferiority randomised trial in 23 teaching and general hospitals in the UK (appendix). Full inclusion and exclusion criteria have been reported previously.⁴ Briefly, adults aged at least 50 years with active, previously untreated neovascular age-related macular degeneration in the eye designated as the study eye and a best corrected distance visual acuity (BCVA) of at least 25 letters on a standard vision chart were eligible to participate.⁴ Participants provided written informed consent. A UK National Health Service Research Ethics Committee approved the trial (07/NIR03/37).

Randomisation and masking

Participants were randomly assigned (1:1:1:1) to one of four groups in a factorial design: ranibizumab or bevacizumab in continuous or discontinuous regimens. Randomisation was stratified by centre and was blocked to ensure roughly equal numbers of participants per group within a centre. 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. Study participants and clinical assessors (nurses, optometrists, imaging technicians, and clinicians) were masked to drug allocation. Study drugs were dispensed by pharmacy staff who were unmasked, but had no other role in the study. Most IVAN sites used a separate unmasked clinical team consisting of a nurse and a clinician to administer treatment; this team did not take part in any other study procedures. At nine sites, staff were insufficient to have masked and unmasked teams; here, an unmasked nurse withdrew ranibizumab from the vial into a syringe so that the final appearance of the preparation was identical to that of the syringe containing prefilled bevacizumab.

All random allocations, including to continuous or discontinuous treatment, were prepared at the outset. Allocation to continuous or discontinuous treatment was masked up to 3 months, at which point both investigator and participant were unmasked. Lesion morphology was assessed by independent graders, who were masked to drug and treatment regimen, in the UK Network of Ophthalmic Reading Centres.

Procedures

Participants received intravitreal injections of ranibizumab (0.5 mg) or bevacizumab (1.25 mg).^{2,10,11} Both drugs were procured commercially. The compounding pharmacy at the Royal Liverpool and Broadgreen University Hospitals NHS Trust (Liverpool, UK) was contracted to supply the study drugs. Bevacizumab was purchased from Roche and prepared for intraocular administration. The pharmacy used a range of standard and non-standard tests to establish stability, potency, and sterility of bevacizumab after aliquoting or storage, or both.^{12,13} Because the most convenient method of dispensing aliquoted bevacizumab is in a prefilled syringe, the drug was stored in sterile polycarbonate syringes, secured with Luer-Lok tip caps for up to 90 days at a temperature of 2–8°C. Stability of the drug was confirmed by tests of molecular weight and electric charge by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) under non-denaturing and denaturing conditions, reverse-phase high-performance liquid chromatography, and size exclusion chromatography. ELISA was used to confirm binding of the drug to VEGF after storage. Tests were done to simulate conditions of transportation, in which syringes were shaken vigorously for up to 6 h at room temperature. The stored drug was subjected to microscopic analysis and culture for microorganisms by serial sampling. The results showed that the drug remained stable and sterile under the conditions described. The pharmacy followed strict standard operating procedures and guidelines for manufacture that were submitted to and approved by the UK Medicines and Healthcare products Regulatory Agency.

Participants underwent clinical examination, optical coherence tomography (OCT), and fundus photography every month (28–35 days). They received study injections at visits 0, 1, and 2. Participants assigned to the continuous regimen were treated monthly thereafter. Participants assigned to the discontinuous regimen were not retreated after visit 2 unless prespecified clinical and OCT criteria for active disease were met.⁴ If retreatment was needed, a further cycle of three doses was given monthly. Prompted by the findings from CATT at 2 years,⁵ colour and OCT images at baseline and most recent available follow-up were regraded after the end of follow-up, specifically to identify any new geographic atrophy lesions that had developed during the trial. Participants were followed up for 2 years. Exit visits before 2 years occurred only when a participant chose to

For the trial protocol see <http://www.hta.ac.uk/1625>

See Online for appendix

leave the study early or was withdrawn by a participating ophthalmologist.

Our objective was to test the non-inferiority of bevacizumab to ranibizumab and of the discontinuous to the continuous regimen. The primary outcome was BCVA (number of letters read on a standard early treatment diabetic retinopathy study chart at 2 years¹⁴). Secondary outcomes were additional visual function measures (contrast sensitivity,¹⁵ near visual acuity,¹⁶ and reading index¹⁷), lesion morphology and metrics from angiograms and OCTs, generic and vision-specific health-related quality of life (EQ-5D,¹⁸ MacDQoL,¹⁹ and MacTSQ²⁰), adverse events, cumulative resource use or cost and cost-effectiveness, and survival free from treatment failure. Results of the cost analyses and for survival free from treatment failure will be reported elsewhere.

BCVA was measured every 3 months. Most of the other outcomes were measured at baseline and visits 3, 6, 12, 18, and 24. Lesion area was measured at baseline, and visits 12 and 24. EQ-5D was measured at baseline, and visits 3, 12, and 24. MacDQoL and MacTSQ were measured at visits 3, 12, and 24.

Adverse events were recorded at each visit and coded with the Medical Dictionary for Regulatory Activities (version 14.1). All SAEs were reviewed by senior clinicians (UC, SPH, SMD, and AJL), who were masked to treatment allocation. The primary safety outcome was the occurrence of an arterial thrombotic event (as defined by the Antiplatelet Trialists' Collaboration²¹) or hospital admission for heart failure.

Statistical analysis

We specified a non-inferiority limit of 3.5 letters for distance BCVA, assuming no interaction between drug and treatment regimen. The target sample size was 600, which would give 90% power to detect non-inferiority (significance 2.5%, one-sided).⁴

Modified intention-to-treat analyses were directed by a prespecified analysis plan. All participants who received at least one dose of allocated drug were included in analyses. We compared drugs and dosing regimens with logistic regression (binary variables) and linear mixed model regression (continuous variables), except when otherwise noted. Analyses were adjusted for centre size (seven strata), combining adjacent strata if necessary to ensure estimation. For continuous variables measured at baseline, we modelled values jointly to avoid having to exclude or impute cases with missing baseline measures. We fitted interactions with follow-up time and describe differences between groups at 2 years. We checked model validity with recommended graphical methods.²² When a model fitted poorly, we explored transformations. Outcomes analysed on a logarithmic scale were transformed back to the original scale after analysis and results are presented as geometric mean ratios. Odds ratios were used for comparisons of EQ-5D, lesion area, and MacTSQ at 2 years, for which we were unable to identify a suitable

transformation; we dichotomised data and adjusted analyses for baseline value when obtained. We compared numbers of SAEs by drug and treatment regimen when more than ten participants experienced the event. We used likelihood ratio tests to establish significance.

Results are reported as effect estimates with 95% CIs. We report comparisons between drugs separately for continuous and discontinuous regimens only when the interaction of drug and dosing regimen reached a prespecified level of significance (5% for total lesion thickness at the fovea and presence of fluid on OCT, for which CATT suggested a possible interaction;³ 1% otherwise).

Previous meta-analyses have been reported.^{23,24} We adapted the search strategy used by Mitchell²⁴ (who identified one head-to-head trial reporting outcomes to 1 year²⁵) and noted that 2-year findings were reported only for CATT.³ We combined changes in BCVA at 2 years from baseline in CATT and the IVAN trial in a fixed-effects meta-analysis. We used weighted mean differences to account for study size. We investigated mortality, arterial thrombotic events, occurrence of at least one serious adverse event, which were all available to only 1 year by treatment regimen for CATT. Additionally, we investigated change in total lesion thickness at the fovea, and new geographic atrophy. We combined changes because the primary CATT analyses reported change analyses. The analyses of the safety data and geographic atrophy used raw frequency counts.

Analyses were done with Stata (version 12.1) and SAS (version 9.3).

This trial is registered, number ISRCTN92166560.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 27, 2008, and Oct 15, 2010, we randomised 628 patients to ranibizumab or bevacizumab. 18 were withdrawn, leaving 610 who received the study drugs and were included in analyses (appendix). Participants' baseline characteristics were similar across the groups (appendix). Nine participants were identified as ineligible after images submitted at time of recruitment were graded, but were nevertheless included.⁴ Ophthalmologists reported not knowing which drug participants were receiving at visit 3 on 555 (98%) of 567 occasions, at visit 12 on 514 (99%) of 521 occasions, at visit 24 on 506 (99%) of 512 occasions, and at exit visit on all 22 occasions. Participants reported not knowing which drug they were receiving at visit 3 on 560 (99%) of 564 occasions, at visit 12 on 509 (99%) of 516 occasions, at visit 24 on 499 (98%) of 510 occasions, and at exit visit on all 21 occasions.

	Ranibizumab (n=271)	Bevacizumab (n=254)	Continuous regimen (n=261)	Discontinuous regimen (n=264)	Overall (n=525)
Best corrected distance visual acuity (letters)*	67.8 (17.0)	66.1 (18.4)	66.6 (17.9)	67.3 (17.5)	67.0 (17.7)
Number of treatments†	18 (11 to 23)	19 (12 to 23)	23 (21 to 24)	13 (8 to 17)	18 (12 to 23)
Near visual acuity (log[minimum angle of resolution])‡	0.55 (0.39)	0.61 (0.42)	0.58 (0.40)	0.58 (0.41)	0.58 (0.41)
Reading index (words read per min divided by print font size)§	50.90 (22.80 to 93.70)	52.50 (9.70 to 90.60)	46.30 (11.40 to 84.00)	55.35 (19.00 to 97.60)	52.00 (15.60 to 93.60)
Reading test not performed due to very poor vision¶	8/249 (3%)	2/235 (1%)	3/245 (1%)	7/239 (3%)	10/484 (2%)
Contrast sensitivity (letters)	28.08 (6.00)	28.30 (5.75)	28.65 (5.40)	27.72 (6.30)	28.19 (5.88)
Total lesion thickness at fovea (µm)**	322.4 (137.3)	331.0 (144.2)	314.7 (137.1)	338.5 (143.3)	326.6 (140.6)
Retinal thickness plus subretinal fluid at fovea (µm)††	163.5 (77.7)	172.7 (95.7)	161.7 (84.2)	174.4 (89.4)	168.0 (87.0)
Any fluid on optical coherence tomography‡‡					
Absent	127/256 (50%)	100/243 (41%)	135/249 (54%)	92/250 (37%)	227/499 (45%)
Present	127/256 (50%)	141/243 (58%)	112/249 (45%)	156/250 (62%)	268/499 (54%)
Cannot grade	2/256 (1%)	2/243 (1%)	2/249 (1%)	2/250 (1%)	4/499 (1%)
Dye leakage on angiogram§§					
Absent	146/250 (58%)	145/236 (61%)	155/244 (64%)	136/242 (56%)	291/486 (60%)
Present	101/250 (40%)	89/236 (38%)	86/244 (35%)	104/242 (43%)	190/486 (39%)
Cannot grade	3/250 (1%)	2/236 (1%)	3/244 (1%)	2/242 (1%)	5/486 (1%)
Neovascular lesion					
Area of lesion (optic disc area) ¶¶¶	0.38 (0.00 to 3.78)	0.43 (0.00 to 3.25)	0.06 (0.00 to 2.87)	0.59 (0.00 to 4.38)	0.39 (0.00 to 3.54)
Present	142/246 (58%)	127/234 (54%)	123/241 (51%)	146/239 (61%)	269/480 (56%)
New geographic atrophy††††	86/305 (28%)	91/291 (31%)	101/301 (34%)	76/295 (26%)	177/596 (30%)
EQ-5D score†††	0.85 (0.73 to 1.00)	0.85 (0.73 to 1.00)	0.85 (0.73 to 1.00)	0.85 (0.73 to 1.00)	0.85 (0.73 to 1.00)
MacDQOL score‡‡‡	-1.5 (-2.8 to -0.3)	-1.4 (-2.7 to -0.4)	-1.3 (-2.7 to -0.3)	-1.6 (-3.0 to -0.4)	-1.4 (-2.7 to -0.3)
MacTSQ score§§§	66 (61.5 to 70.0)	65 (60.0 to 69.0)	65.5 (61.0 to 69.0)	66 (60.0 to 69.0)	66 (61.0 to 69.0)

Data are mean (SD), median (IQR), or n/N (%). 525 patients who reached visit 24 at 2 years included, unless otherwise stated. *Data missing for eight patients (one given ranibizumab in continuous regimen; two given ranibizumab in discontinuous regimen; one given bevacizumab in continuous regimen; four given bevacizumab in discontinuous regimen). †All study participants (n=610) included in analysis. ‡Data missing for 26 patients (six; nine; five; six). §Data missing for 41 patients (nine; 13; seven; 12). ¶Log(minimum angle of resolution)=1.6. ||Data missing for 21 patients (four; seven; four; six). **Data missing for 30 patients (six; 11; eight; five). ††Data missing for 30 patients (six; 11; eight; five). ‡‡Data missing for 26 patients (six; nine; six; five). §§Data missing for 39 patients (nine; 12; eight; ten). ¶¶Includes lesions with zero area (ie, not present); data missing for 45 patients (11; 14; nine; 11). ||||Number of eyes with non-zero lesion area. ***Data missing for 14 patients (six; three; one; four). †††Data missing for 11 patients (two; two; three; four). ‡‡‡Score ranges from -9 (maximum negative effect) to 3 (maximum positive effect); data missing for 91 patients (25; 20; 24; 22). §§§Score ranges from 0 to 72 (higher scores indicate higher satisfaction with treatment); data missing for 107 patients (29; 22; 28; 28).

Table 1: Outcomes at 2 years

Some protocol deviations were recorded (appendix). The wrong study drug was given on two (<1%) of 12761 follow-up visits, and treatment regimens were not adhered to on 133 visits (1%). Overall, 350 participants (57%) missed at least one visit, including those who died or withdrew early. However, 12761 (87%) of 14640 scheduled visits were attended, and the analysis methods meant that most participants could be included.

525 participants reached the visit at 2 years (table 1). BCVA at 2 years was similar between ranibizumab and bevacizumab groups and continuous and discontinuous treatment groups (table 1). Bevacizumab was neither inferior nor non-inferior to ranibizumab because the 95% CIs include zero and the non-inferiority margin (figure 1). Similarly the discontinuous regimen was neither inferior nor non-inferior to the continuous regimen. Therefore, the primary hypotheses about the non-inferiority of discontinuous bevacizumab to continuous ranibizumab were not supported.

Near visual acuity, reading index, and contrast sensitivity after 2 years did not differ significantly between

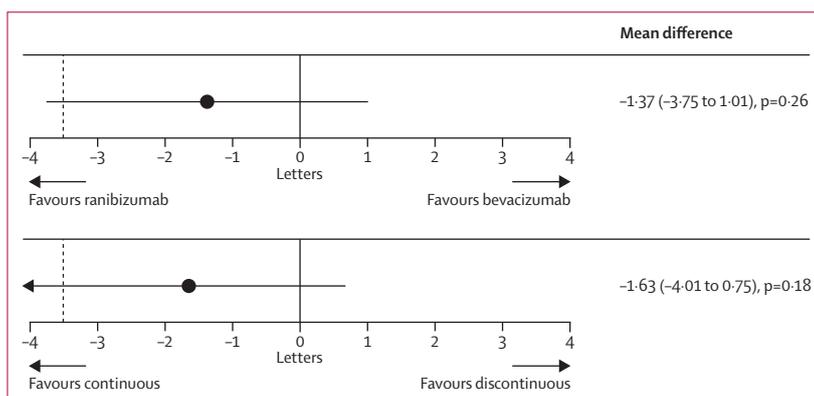


Figure 1: Mean differences in best corrected distance visual acuity at 2 years
By drug (top) and by regimen (bottom). Black dashed line shows non-inferiority limit of -3.5 letters. Mean differences estimated with data from visits 0, 3, 6, 9, 12, 15, 18, 21, and 24, adjusted for centre size. 95% CIs given in parentheses and shown by bars.

drug groups (figure 2, table 1). However, near visual acuity and contrast sensitivity were significantly worse with the discontinuous regimen (figure 2, table 1). Total

lesion thickness and the neurosensory retinal thickness including subretinal fluid did not differ significantly between drug groups but were significantly lower for participants assigned to continuous regimens than discontinuous regimens (figure 2, table 1). The percentage of participants with fluid on OCT at 2 years was higher in the bevacizumab group than in the ranibizumab group

(table 1), but the difference was not significant (figure 2). The percentage was significantly higher in the discontinuous treatment group than in the continuous treatment group (figure 2, table 1). Significantly more participants in the discontinuous treatment group than the continuous treatment group had an active neovascular lesion at 2 years, but drug groups did not differ

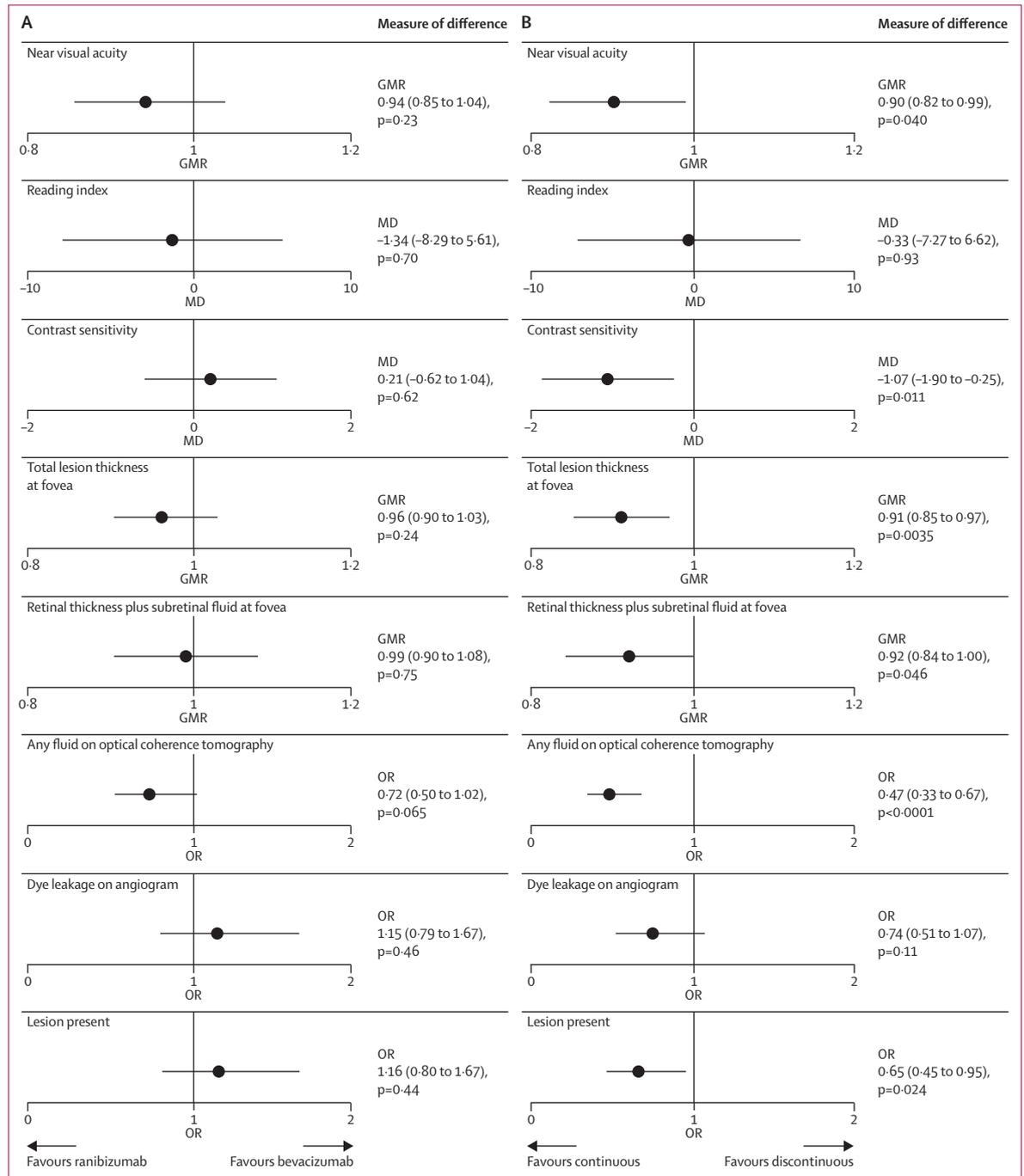


Figure 2: Secondary outcomes at 2 years (A) By drug. (B) By regimen. 95% CIs given in parentheses and shown by bars. GMR=geometric mean ratio. MD=mean difference. OR=odds ratio.

(figure 2, table 1). The percentage of participants with new geographic atrophy did not differ between drug groups (odds ratio [OR] 0·87, 95% CI 0·61–1·25; $p=0\cdot46$), but was significantly lower in participants on discontinuous regimens than on continuous regimens (1·47, 1·03–2·11; $p=0\cdot03$; table 1). Median MacDQoL, MacTSQ, and EQ-5D state scores did not differ by drug (MacDQoL:

$p=0\cdot74$; MacTSQ: $p=0\cdot23$; EQ-5D: $p=0\cdot51$; appendix) or treatment regimen ($p=0\cdot73$; $p=0\cdot47$; $p=0\cdot64$; appendix).

2 years after randomisation, the frequency of death (OR 0·96, 95% CI 0·46–2·02; $p=0\cdot91$) or of an arterial thrombotic event or hospital admission for heart failure (1·69, 0·80–3·57; $p=0\cdot16$) did not differ between drug groups (table 2, appendix). However, significantly more

	Ranibizumab (n=314)		Bevacizumab (n=296)		Continuous regimen (n=308)		Discontinuous regimen (n=302)		Overall (n=610)	
	Number of events	Affected patients	Number of events	Affected patients	Number of events	Affected patients	Number of events	Affected patients	Number of events	Affected patients
Serious systemic event										
Death by any cause*	15	15 (5%)	15	15 (5%)	10	10 (3%)	20	20 (7%)	30	30 (5%)
Arterial thrombotic event	13	13 (4%)	12	10 (3%)	7	7 (2%)	18	16 (5%)	25	23 (4%)
Non-fatal myocardial infarction†	4	4 (1%)	5	4 (1%)	2	2 (1%)	7	6 (2%)	9	8 (1%)
Non-fatal stroke	6	6 (2%)	3	3 (1%)	4	4 (1%)	5	5 (2%)	9	9 (1%)
Death from vascular causes	3	3 (1%)	4	4 (1%)	1	1 (<1%)	6	6 (2%)	7	7 (1%)
Arterial thrombotic event or heart failure	20	20 (6%)	14	12 (4%)	12	12 (4%)	22	20 (7%)	34	32 (5%)
Heart failure	7	7 (2%)	2	2 (1%)	5	5 (2%)	4	4 (1%)	9	9 (1%)
Venous thrombotic event	3	3 (1%)	4	4 (1%)	3	3 (1%)	4	4 (1%)	7	7 (1%)
Deep vein thrombosis	0	0	1	1 (<1%)	0	0	1	1 (<1%)	1	1 (<1%)
Pulmonary embolism	3	3 (1%)	3	3 (1%)	3	3 (1%)	3	3 (1%)	6	6 (1%)
Hospital admission for angina	7	7 (2%)	3	3 (1%)	6	6 (2%)	4	4 (1%)	10	10 (2%)
Hospital admission for non-ocular haemorrhage	3	3 (1%)	1	1 (<1%)	2	2 (1%)	2	2 (1%)	4	4 (1%)
Transient ischaemic attack‡	1	1 (<1%)	1	1 (<1%)	0	0	2	2 (1%)	2	2 (<1%)
Any serious systemic event excluding non-vascular deaths	..	31 (10%)	..	19 (6%)	..	21 (7%)	..	29 (10%)	..	50 (8%)
Any serious systemic event including non-vascular deaths	..	38 (12%)	..	28 (9%)	..	27 (9%)	..	39 (13%)	..	66 (11%)
≥1 serious systemic event§	..	81 (26%)	..	80 (27%)	..	74 (24%)	..	87 (29%)	..	161 (26%)
MedDRA system organ class										
Cardiac disorders¶	20	20 (6%)	20	19 (6%)	16	16 (5%)	24	23 (8%)	40	39 (6%)
Gastrointestinal disorders	3	3 (1%)	10	9 (3%)	7	6 (2%)	6	6 (2%)	13	12 (2%)
General disorders and administration site conditions	15	15 (5%)	16	16 (5%)	10	10 (3%)	21	21 (7%)	31	31 (5%)
Infections and infestations	10	9 (3%)	16	12 (4%)	13	10 (3%)	13	11 (4%)	26	21 (3%)
Injury, poisoning, and procedural complications	12	12 (4%)	10	10 (3%)	10	10 (3%)	12	12 (4%)	22	22 (4%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)**	11	11 (4%)	16	14 (5%)	11	11 (4%)	16	14 (5%)	27	25 (4%)
Nervous system disorders	9	9 (3%)	8	8 (3%)	5	5 (2%)	12	12 (4%)	17	17 (3%)
Respiratory, thoracic, and mediastinal disorders††	9	8 (3%)	7	7 (2%)	9	8 (3%)	7	7 (2%)	16	15 (2%)
Surgical and medical procedures‡‡	16	16 (5%)	14	14 (5%)	14	14 (5%)	16	16 (5%)	30	30 (5%)
Vascular disorders	6	5 (2%)	6	6 (2%)	4	4 (1%)	8	7 (2%)	12	11 (2%)
Other	14	12 (4%)	15	14 (5%)	11	10 (3%)	18	16 (5%)	29	26 (4%)
Ocular event in the study eye										
Uveitis	0	0	1	1 (<1%)	1	1 (<1%)	0	0	1	1 (<1%)
Retinal detachment	1	1 (<1%)	0	0	0	0	1	1 (<1%)	1	1 (<1%)
Cataract traumatic	1	1 (<1%)	1	1 (<1%)	1	1 (<1%)	1	1 (<1%)	2	2 (<1%)
Retinal pigment epithelial tear	3	3 (1%)	1	1 (<1%)	2	2 (1%)	2	2 (1%)	4	4 (1%)
Other	5	4 (1%)	3	3 (1%)	2	2 (1%)	6	5 (2%)	8	7 (1%)
≥1 ocular event	..	8 (3%)	..	6 (2%)	..	6 (2%)	..	8 (3%)	..	14 (2%)
Any serious adverse event	..	87 (28%)	..	84 (28%)	..	79 (26%)	..	92 (30%)	..	171 (28%)

Data are n or n (%). MedDRA=Medical Dictionary for Regulatory Activities. *Two in bevacizumab discontinuous group occurred >3 months after last visit. †One in bevacizumab discontinuous group occurred >3 months after last visit. ‡Not defined as an expected serious adverse event in the protocol. §Includes any non-ocular serious adverse event. ¶One in bevacizumab discontinuous group occurred >105 days after last visit. ||Three in bevacizumab discontinuous group occurred >105 days after last visit. **One in bevacizumab discontinuous group occurred >105 days after last visit. ††One in bevacizumab discontinuous group occurred >105 days after last visit. ‡‡One in ranibizumab discontinuous group occurred >105 days after last visit.

Table 2: Serious adverse events within 2 years of recruitment

patients on the discontinuous regimen than on the continuous regimen had died (OR 0.47, 95% CI 0.22–1.03; $p=0.05$), although no difference by regimen

between frequency of an arterial thrombotic event or heart failure was recorded (0.56, 0.27–1.19; $p=0.13$; table 2, appendix).

Similar percentages of participants in the drug groups had at least one systemic SAE ($p=0.82$; table 2, appendix). Tests of the frequency of SAEs in different organ systems when there were more than ten participant-specific events showed that SAEs coded as general disorders and administration site conditions (which includes all deaths) differed by treatment regimen ($p=0.03$) but not for any other organ system by drug or treatment regimen (table 2, appendix). SAEs coded as gastrointestinal were more frequent with bevacizumab than with ranibizumab (table 2), but the difference was not significant ($p=0.06$; appendix) and was less than at 1 year.⁴ Serious ocular adverse events were rare (table 2, appendix).

The BCVA point estimate with pooled IVAN and CATT data showed that bevacizumab was non-inferior to ranibizumab, judged by the strict IVAN non-inferiority margin of 3.5 letters (figure 3). Although the as needed treatment regimens differed slightly, we decided to pool data for the two trials for this comparison. The discontinuous regimen was inferior to the continuous regimen (figure 3). Pooled estimates of changes in total lesion thickness at the fovea showed no difference between drugs, but favoured continuous treatment ($p=0.001$; appendix). New geographic atrophy was detected significantly more often during follow-up in participants on continuous than discontinuous regimens, but no difference between drugs was recorded ($p=0.001$; figure 4). Pooled estimates of safety outcomes showed no differences by drug for deaths or arterial thrombotic events but a significantly increased risk of any systemic SAE for bevacizumab ($p=0.008$; figure 5). The comparison by regimen showed consistent increases in mortality ($p=0.014$) and the risk of any systemic SAE ($p=0.063$) with discontinuous treatment across trials (figure 5).

Discussion

After 2 years in the IVAN trial, neither the comparison of bevacizumab with ranibizumab nor that of continuous with discontinuous regimens for BCVA was conclusive when judged against the prespecified non-inferiority margin of 3.5 letters. However, the mean differences between groups, tending to favour ranibizumab and continuous treatment, were small and estimated to within 2.4 letters. Non-inferiority for both comparisons would have been established had we used the CATT non-inferiority margin of 5 letters. When we examined the pooled IVAN and CATT findings for BCVA, the point estimates were consistent. The increased precision gained with pooled data showed that bevacizumab was non-inferior to ranibizumab, but that discontinuous treatment was inferior to continuous treatment (panel). Nevertheless, even in the comparison between treatment regimens, the pooled mean difference was small from a clinical perspective.

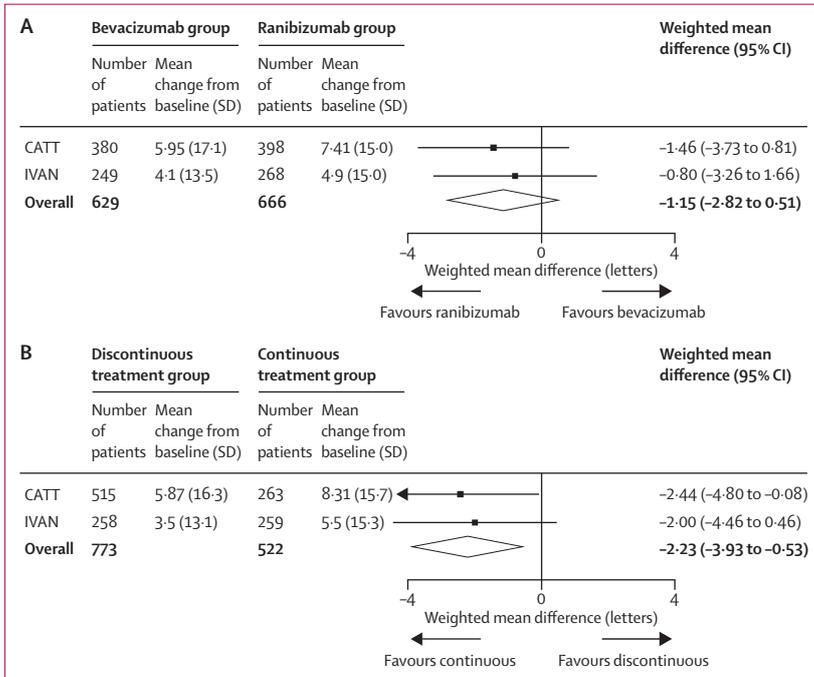


Figure 3: Change in best corrected distance visual acuity in CATT and IVAN at 2 years
(A) By drug. (B) By regimen. 95% CIs shown by bars. CATT=Comparison of Age-related macular degeneration Treatment Trials. IVAN=Inhibition of VEGF in Age-related choroidal Neovascularisation trial.

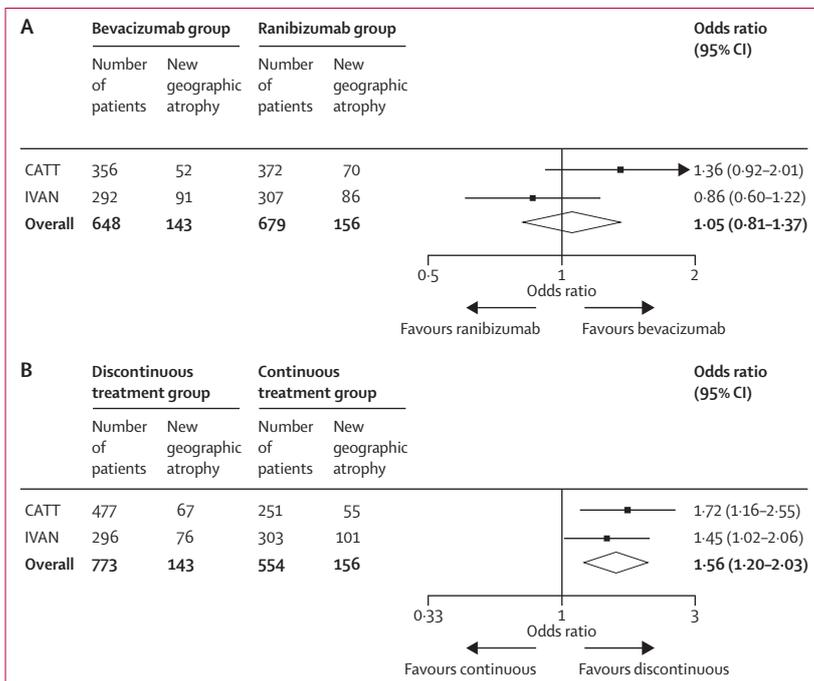


Figure 4: Geographic atrophy in CATT and IVAN at 2 years
(A) By drug. (B) By regimen. 95% CIs shown by bars. CATT=Comparison of Age-related macular degeneration Treatment Trials. IVAN=Inhibition of VEGF in Age-related choroidal Neovascularisation trial.

With respect to lesion morphology, we identified no significant differences between drugs at 2 years, but consistent differences favouring continuous treatment. The meta-analysis of total lesion thickness at the fovea confirmed these findings. Similar to the lesion metrics, we recorded no differences in quality of life by drug, but near visual acuity and contrast sensitivity favoured a continuous regimen. Overall, the findings for the IVAN secondary visual function outcomes and the pooled findings for BCVA and lesion morphology consistently show that bevacizumab has similar efficacy to ranibizumab. The findings also suggest that continuous treatment every month gives slightly better visual function than does discontinuous treatment, although this improvement was not reflected in the primary outcome of BCVA or in self-reported health-related quality of life.

The CATT 2-year report⁵ suggested differences between drugs and treatment regimens in the development of new geographic atrophy in the study eye during follow-up. We found no difference between drugs in the IVAN trial alone and when CATT and IVAN data were combined. However, our analysis showed a consistent and substantial increase in the risk of developing new geographic atrophy with monthly compared with discontinuous treatment. This finding raises the worrying possibility that any visual benefit from monthly treatment might not be maintained in the long term.

For safety outcomes, our finding that mortality was higher at 2 years with discontinuous treatment than continuous treatment is similar to the 1-year findings in CATT (pooled OR 0.49; $p=0.014$), as is increase in the risk of any systemic SAE (0.81; $p=0.063$). The comparisons of discontinuous and continuous regimens were not masked in either trial, but it seems implausible that bias should lead to an increased frequency of SAEs with discontinuous treatment. These worrying findings appear counterintuitive when viewed in a conventional dose-response framework. However, in the context of biological therapies, the possibility of immunological sensitisation with intermittent dosing needs to be considered.²⁸

Neither the IVAN trial nor CATT was powered to detect differences in harms of treatment. Hence, the meta-analyses provide the best summary of the available data. The comparisons between the drugs after 2 years are reassuring, with no suggestion of any difference in mortality or arterial thrombotic events, which have previously been suggested to be related to use of anti-VEGF drugs. The pooled analysis for any systemic SAE seems to confirm an increased risk with bevacizumab, which was first reported in CATT.^{3,5} However, the pooled analysis disguises the inconsistency between the separate trial estimates. Although the trials had similar findings at 1 year,⁴ the SAEs accruing in the second year in the IVAN trial shifted the 2-year OR almost to unity. Other findings for cardiovascular arterial thrombotic events from large analyses of routinely obtained data also vary²⁹⁻³¹ and are

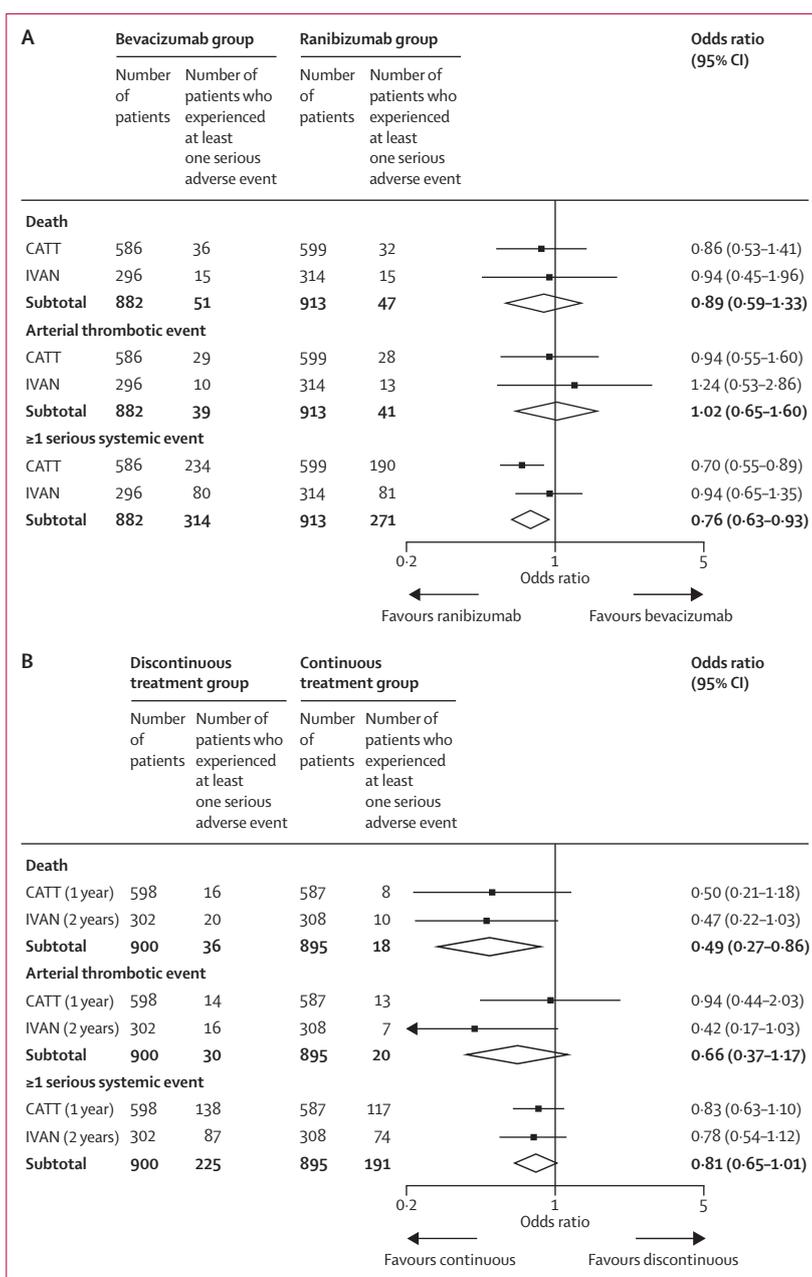


Figure 5: Safety outcomes in CATT and IVAN at 2 years
 (A) By drug. (B) By regimen. 95% CIs shown by bars. CATT=Comparison of Age-related macular degeneration Treatment Trials. IVAN=Inhibition of VEGF in Age-related choroidal Neovascularisation trial.

at risk of confounding.³² Differences between trials in masking of participants to drug allocation, which was achieved reliably only in the IVAN trial, could be a possible explanation. The accruing SAEs in our trial also provided improved precision for the pooled comparison by treatment regimen (IVAN 2-year and CATT 1-year data), showing a significant difference in mortality favouring continuous treatment, which is probably the finding of greatest concern.

Panel: Research in context**Systematic review**

We searched PubMed for reports of previous head-to-head trials with the terms "ranibizumab" (MeSH term or text), "bevacizumab" (MeSH term or text), and "macular degeneration" (major MeSH term), published in any language before July 3, 2013. We included only clinical or randomised controlled trials and identified systematic reviews comparing ranibizumab and bevacizumab. We searched Current Controlled Trials across several trial registers ("macular degeneration" and "ranibizumab", "bevacizumab", or "VEGF" in the title). We identified three trials other than CATT and the IVAN trial in which bevacizumab and ranibizumab have previously been compared.²⁵⁻²⁷ Two were single-centre trials^{25,27} and one a multicentre trial (the MANTA study²⁶), but findings at 2 years had not been reported. Therefore, we only included the CATT and IVAN data in our meta-analyses.

Interpretation

IVAN and CATT are the first and largest multicentre head-to-head trials in which bevacizumab and ranibizumab for neovascular age-related macular degeneration have been compared. After 2 years in the IVAN trial, the comparisons of the effect of the drugs and of discontinuous versus continuous treatment on best corrected visual acuity were inconclusive. However, when we pooled data from the two trials, bevacizumab was non-inferior to ranibizumab. It is now established that bevacizumab is not inferior to ranibizumab after 2 years of either continuous or discontinuous treatment with respect to visual acuity, and that total lesion thickness is also not significantly different by drug. With respect to systemic safety, there is no suggestion of any difference between drugs in deaths or arterial thrombotic events at 2 years. As far as we are aware, visual function and safety with continuous versus discontinuous treatment has been compared only in CATT and the IVAN trial. Pooled data from the two trials shows that discontinuous treatment was inferior to continuous treatment for best corrected visual acuity. However, this difference is not clinically important. There was a significant difference in mortality favouring continuous treatment. Conversely, the risk of geographic atrophy increased with continuous treatment. The trade-offs should be discussed with patients. Overall, the available data show that the choice of anti-VEGF treatment strategy for neovascular age-related macular degeneration is less straightforward than previously thought. Bevacizumab and ranibizumab have similar efficacy, but the difference in mortality favouring continuous treatment means that continuous treatment might be preferable.

Our trial has important strengths. It was pragmatic, being done in the usual care setting in many hospitals in the UK National Health Service, and so directly informs the use of anti-VEGF drugs in similar settings. The bevacizumab product used in this trial was sourced from a compounding pharmacy that aliquoted and dispensed the drug, adhering to protocols for tests of potency and sterility approved by the Medicines and Healthcare products Regulatory Agency. Our findings should be generalised only to bevacizumab sourced from a manufacturing pharmacy that has quality-control processes to validate stability, potency, and sterility that have been approved by a drug regulatory agency.

The factorial design was efficient and provided high statistical power for the primary outcome, despite the fact that the IVAN trial had only half as many participants as CATT. We studied a range of secondary functional outcomes that both support the visual acuity findings and describe the compromises when treatment is not continuous. We assessed the resources used to

administer treatment and previously reported that they were similar with either drug.⁴ Drug allocation was successfully masked and, in view of the elderly trial population, we had good retention. Sites failed to comply with the allocated treatment on only roughly 1% of visits (almost always relating to the treatment regimen) and, although most patients missed one or more visits, missed visits did not differ by group and most scheduled visits were attended.

The interpretation of the meta-analyses is limited by the appropriateness of pooling of available trials.³³ We argue that, in this instance, the pooling of data was appropriate, because the studies were planned to be similar in design. We described our intention to pool data from the two trials in advance, and the CIs for the estimates from the studies overlap in all reported meta-analyses. The meta-analyses of safety particularly were prompted by the IVAN and CATT data monitoring committees. Our descriptions of results from the two trials as consistent or inconsistent are subjective judgments on the basis of the meta-analysis graphs.

Anti-VEGF drugs look set to remain the mainstay treatment for neovascular age-related macular degeneration for the foreseeable future, despite the rapid increase in potential new treatments. Concerns have been raised about the safety of aflibercept,³⁴ despite evidence of efficacy,⁶ and the results of brachytherapy in combination with anti-VEGF drugs have, so far, been disappointing.³⁵ Photodynamic therapy or radiotherapy options used in combination might yet allow reductions in treatment frequency, but it will be important to study these treatment strategies in comparison with monthly treatment, in view of our finding of possible risks of discontinuous treatment.

In conclusion, the IVAN trial and meta-analyses of the CATT and IVAN data show that the choice of anti-VEGF treatment strategy is less straightforward than previously thought. Bevacizumab and ranibizumab have similar efficacy and can be considered equivalent in this respect in the treatment of neovascular age-related macular degeneration. The increased risk of systemic SAEs and death with discontinuous treatment should probably outweigh the increased risk of new geographic atrophy that was recorded with monthly treatment. The slightly better functional outcomes with continuous treatment are a bonus. Continuous treatment also avoids the need to monitor disease activity on every visit. An important consideration when choosing to give treatment continuously is the high cost of ranibizumab,⁴ which may be unaffordable for publicly funded health systems.

Contributors

All members of the writing committee, except LAC, obtained funding to design the trial and formed part of the Trial Management Group overseeing trial conduct. UC was the chief investigator with overall responsibility for the trial. UC and SPH managed the UK Network of Ophthalmic Reading Centres. UC, SPH, and BCR designed the trial. CAR specified and supervised the statistical analyses. UC, SPH, SMD, and AJL led recruitment, site selection, addressed clinical queries, and reviewed

adverse events. LAC was the trial manager and implemented the trial protocol, developing and refining trial procedures to optimise its conduct. UC, CAR, and BCR wrote the first draft of the report. All authors contributed to the final draft and approved its submission for publication.

Conflicts of interest

UC, SPH, and AJL are principal investigators of trials sponsored by Novartis, the manufacturers of ranibizumab. UC has attended and been remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan, and Bausch and Lomb; and her employing institution has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and Pfizer. CAR has received an honorarium from Novartis for a lecture. SMD's and AJL's employing institutions have received payments from Novartis. SMD and AJL have received honoraria from Novartis for lectures. AJL has attended and been remunerated for attendance at advisory boards for Novartis and Bayer. BCR has received a fee for teaching from Janssen-Cilag. LAC declares that she has no conflicts of interest.

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