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Serious Adverse Events with Bevacizumab or Ranibizumab for Age-related Macular Degeneration: Meta-analysis of Individual Patient Data

The Bevacizumab-Ranibizumab International Trials Group ‡

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This article contain additional online-only material. The following should appear online-only: Appendix and Figures 2 to 5.

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Running head: Meta-analysis of safety of bevacizumab and ranibizumab

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ABSTRACT

Topic: A comparison between ranibizumab and bevacizumab of the incidence of systemic serious adverse events (SAEs) among patients with neovascular age-related macular degeneration (nAMD) who participated in a large-scale randomized trial. Use of individual patient data, rather than aggregate data, allowed adjustment for strong predictors of SAEs.

Clinical relevance: Relative safety of ranibizumab and bevacizumab is important in choosing an anti-VEGF drug for the hundreds of thousands of patients with nAMD treated each year worldwide.

Methods: Results of a Cochrane aggregate meta-analysis of the relative efficacy and safety of bevacizumab and ranibizumab that used searches of bibliographic databases and clinical trial registries as of March 14, 2014 and hand searching were reviewed to identify 6 large-scale, multicenter clinical trials. Individual patient data on SAEs, assigned drug and dosing regimen, and baseline prognostic factors were requested from the leaders of the 6 trials. A two-stage approach was used to estimate relative risks and 95% confidence intervals (CIs) from Cox proportional hazards models adjusting for baseline prognostic factors. The primary outcome measure was development of ≥1 SAE; secondary outcome measures were death, arteriothrombotic events, events associated with systemic anti-VEGF therapy, and events not associated with systemic anti-VEGF therapy.

Results: Individual patient data were received from 5 trials to provide information on 3052 patients. There were no large imbalances between drug groups on baseline factors. The adjusted relative risk (95% CI) for bevacizumab relative to ranibizumab was 1.06 [(0.84, 1.35); p=0.61] for ≥1 SAEs. For secondary outcomes, adjusted relative risks were 0.99 [(0.69, 1.43); p=0.97] for death, 0.89 [(0.62, 1.28); p=0.53] for arteriothrombotic events, 1.10 [(0.81, 1.50); p=0.54] for events related to anti-VEGF treatment, and 1.11 [(0.87, 1.40); p=0.40] for events not related to anti-VEGF treatment.

Conclusion: Our findings support the absence of large differences in risk of systemic serious adverse events between these two anti-VEGF drugs; i.e., relative risks of ≥1.5 are unlikely. Because additional head-to-head trials are unlikely, any further investigation of differential risk between anti-VEGF agents will only be achieved though post-marketing surveillance or through the interrogation of healthcare databases.

The management and prognosis of patients with neovascular age-related macular degeneration (AMD) changed dramatically in 2005 with the release of results from Phase III clinical trials of intravitreally administered ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), an inhibitor of all active forms of vascular endothelial growth factor (VEGF).[1,2] On average, eyes treated with ranibizumab gained visual acuity while untreated eyes or eyes treated with photodynamic laser therapy lost substantial visual acuity. While waiting for approval from regulatory agencies in the United States and Europe, ophthalmologists began using intravitreal bevacizumab off label to treat neovascular AMD because it was structurally similar to ranibizumab (Avastin; Genentech, Inc., South San Francisco, CA), available for use because it had been approved for treatment of cancer, and was inexpensive. Short-term outcomes related to vision and retinal morphology after treatment with bevacizumab appeared similar to those of ranibizumab, leading to rapid adoption of bevacizumab as first-line therapy. The fact that after ranibizumab was approved by the Food and Drug Administration, ranibizumab was sold for approximately $2000 per dose in the United States compared to $50 for bevacizumab, amplified the need for comparison of longer term efficacy and safety between the two drugs.[3]

Planning for large-scale, multicenter clinical trials of the two drugs was initiated in 6 different countries. These multicenter clinical trials were: the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) in the United States, the Alternative Treatments to Inhibit VEGF in Age-related Choroidal Neovascularization (IVAN) in the United Kingdom, the Groupe d'Etude Français Avastin versus Lucentis dans la DMLA néovasculaire (GEFAL) in France, the Multicenter Anti-VEGF Trial in Austria (MANTA), Lucentis Compared to Avastin Study (LUCAS) in Norway, and Bevacizumab and Ranibizumab in Age-related Macular Degeneration (BRAMD) in the Netherlands.[4-12] In 2011, CATT was the first of the trials to provide 1-year results.[4] The mean change in visual acuity under treatment with bevacizumab was non-inferior to the mean change in visual acuity under treatment with ranibizumab. The results on efficacy from the other multicenter clinical trials have been consistent with no

difference or only a small difference in change in visual acuity between drugs after the initiation of treatment; a recent meta-analysis yielded a mean difference (95% confidence interval [CI]) of -0.5 letters (-1.6 to +0.6), with a negative difference indicating less improvement in eyes treated with bevacizumab.[13]

However, the results from one of the clinical trials raised concerns on the safety of bevacizumab relative to ranibizumab. In CATT, the proportion of patients with 1 or more systemic serious adverse events (SAEs) at 1 year was higher with bevacizumab than ranibizumab (24.1% vs. 19.0%; adjusted relative risk, 1.29; 95% CI [1.01, 1.66]) and the elevated risk persisted at 2 years (39.9% vs. 31.7%; adjusted relative risk, 1.30; 95% CI [1.07, 1.57]; P=0.009).[4,5] Rates of death and arteriothrombotic events were similar for the two drugs. As the results from other clinical trials became available, several groups of investigators performed meta-analyses of overall SAEs and specific adverse events based on the aggregate data.[13-19] The most comprehensive analysis of SAEs was a Cochrane review led by Moja consisting of 3665 patients with 3356 from the 6 multicenter clinical trials noted above and 309 patients from 3 smaller-scale studies.[15] The combined risk ratio for 1 or more systemic adverse events was 1.08, 95% CI (0.90, 1.31). Similar to the researchers conducting previous meta-analyses, Moja et al concluded that there was no strong evidence of a difference in risk but that the data available was not sufficient to rule out clinically important differential risks, particularly for specific adverse events.

The purpose of the present investigation was to use individual patient data, rather than aggregate data, from the large-scale multicenter clinical trials evaluating bevacizumab and ranibizumab for treatment of neovascular age-related macular degeneration to estimate the relative risk of serious systemic adverse events and selected specific SAEs adjusted for prognostic baseline variables. Although randomization is expected to provide treatment groups that are balanced on predisposing conditions, small imbalances on strong prognostic factors such as age, smoking, hypertension, and use of anti-coagulant medications can artificially

inflate or deflate the difference in risk between the two drugs. Accounting for covariates also may increase the precision of the estimates of the relative risk.

METHODS

Clinical Trials Included

Investigators for a recent Cochrane aggregate meta-analysis of the relative efficacy and safety of intravitreal bevacizumab and ranibizumab searched electronic bibliographic databases and clinical trial registries as of March 14, 2014 and used hand searching to identify 5249 records that might address the topic.[13] Nine trials were identified by the Cochrane investigators. We targeted for this review the six multicenter, randomized clinical trials that compared bevacizumab to ranibizumab, reported counts for patients with 1 or more SAEs, had at least 1 patient reported to have an SAE, and had results published or presented at a national meeting by December 2015. Eligibility criteria for all the trials specified enrollment of eyes with active neovascularization.

Specification of Outcomes and Effect Measures

The primary outcome for the review was the percentage of patients experiencing 1 or more SAEs as defined by the Food and Drug Administration of the United States and the European Medicines Agency.[20,21] This definition includes all deaths, life-threatening events, hospitalizations, events resulting in persistent or significant disability, important medical events, and congenital anomalies. Secondary outcomes were the specific SAEs of death, arteriothrombotic events as defined by the Antiplatelet Trialists' Collaboration (APTC), events previously associated with systemic anti-VEGF treatment (arteriothrombotic events [including but not limited to myocardial, cerebellar, and cerebral ischemia and infarction, coronary artery occlusion, transient ischemic attack, cerebrovascular accidents, and embolism], systemic hemorrhage [including duodenal, gastric, gastrointestinal, rectal, respiratory tract, urogenital, cerebral, intracranial hemorrhage and hematoma], cardiac failure [including congestive heart failure], venous thrombotic events [including pulmonary embolism, deep vein thrombosis, and

thrombosis], hypertension [including hypertensive heart disease and accelerated hypertension], vascular death), and events not previously associated with systemic anti-VEGF treatment.[22-24] Because of an imbalance reported from CATT, gastrointestinal hemorrhages were also summarized. The difference in risk was summarized by the relative risk (hazard ratio) and the associated 95% confidence interval.

Data Collection and Statistical Analysis

The Coordinating Center for CATT managed the data and performed the statistical analyses for the review. The lead author or primary contact person as listed in a registry of clinical trials was invited to provide individual patient data. Data were to be provided in two electronic data files containing only de-identified data. The first file contained age at enrollment, gender, drug (bevacizumab or ranibizumab), dosing regimen (pro re nata, monthly, or treat-and-extend), study eye (right or left), smoking status at baseline (current, past, or never), diabetes at baseline (yes or no), use of medications for hypertension at baseline (yes or no), treatment of the fellow eye with anti-VEGF drugs during the study period (drug and duration of use), use of aspirin at baseline (yes or no), use of an anti-coagulant at baseline (yes or no), and number of days between enrollment and the last date of data collection for SAEs. The individual patient characteristics at baseline were chosen because they are known to be strong prognostic factors for one or more of the outcomes of interest. The second file contained one record for each SAE and included the number of days between study enrollment and the SAE, the Medical Dictionary for Regulatory Activities (MedDRA) code number, and MedDRA preferred term for the SAE. The period of observation was 2 years after study entry for CATT and IVAN and 1 year for the other 4 studies.

A two-stage approach was used for each meta-analysis.[25,26] In the first stage, a Cox proportional hazards model of the outcome of interest was used for each individual clinical trial to provide a relative risk adjusted for baseline prognostic factors and to provide the associated 95% confidence interval for the risk of using bevacizumab compared to using ranibizumab.

212 Only the first observation of the outcome of interest was included in the analysis. The Cox
213 models included dosing regimen (for CATT and IVAN only because these trials include both
214 monthly and as-needed regimens), age, gender, smoking status, diabetes status, use of
215 medications for or a diagnosis of hypertension, use of aspirin, and use of anti-coagulants when
216 data for these variables were available. For the second stage, OpenMeta[Analyst] statistical
217 software for meta-analyses was used to produce a weighted average of the trial specific relative
218 risk from the first stage (http://www.cebm.brown.edu/open_meta/ accessed 10/20/2015).
219 Random effects models using maximum likelihood estimation were chosen to reflect both the
220 within-study variability (95% CIs estimated in stage 1) and the between-study variability (the
221 difference between the point estimates from stage 1 and the pooled estimate).[27] Heterogeneity
222 among trial results was evaluated with the I^2 statistic. For purposes of comparison, an
223 unadjusted meta-analysis was performed with OpenMeta[Analyst] using aggregate data as for
224 stage 2 of the adjusted meta-analysis. Individual patient data were not provided from MANTA.[9]
225 As a secondary analysis, the unadjusted risk estimates for 1 or more SAEs and for death from
226 based on the publication of 1-year MANTA results were used for the second stage of the
227 adjusted meta-analysis. Because the conversion from the published data to the other outcomes
228 of interest could not be made without more details on type of the SAEs, no secondary analyses
229 were performed for the other outcomes of interest.
230 The data files from the 5 clinical trial groups providing individual patient data were checked
231 for completeness of the data requested and for consistency with published aggregate results.
232 Data files for CATT, IVAN, GEFAL, and LUCAS, matched the published aggregate findings for
233 the safety analysis with respect to number of patients and number of patients with 1 or more
234 systemic SAE in each treatment group. Serious ocular adverse events were not counted as
235 systemic adverse events for this analysis.[11] There was 1 less patient assigned to bevacizumab
236 in the data files from BRAMD than reported in published results.[12] Nine patients in LUCAS, who
237 had no serious adverse events, were excluded from the efficacy analysis in LUCAS because of

serious non-compliance with the treatment protocol and were excluded from the adjusted analysis in this report. When data on use of medications for hypertension were not available, data on a diagnosis of hypertension were used instead.

RESULTS

The baseline data available from each clinical trial are summarized in Table 1. Among the five clinical trials providing individual patient data, age, gender, diabetes status, and hypertension status (as defined in the parent trial) were available in all trials. There were only small imbalances between the bevacizumab and ranibizumab groups on the baseline characteristics.

There were 403 (26.6%) patients among 1513 treated with bevacizumab and 366 (23.8%) among 1539 treated with ranibizumab who had 1 or more systemic SAE. The numbers of patients in each treatment group in each study are provided in Table 2. Adjusted meta-analysis results are shown in Figure 1 and compared to the unadjusted results in Table 3. The pooled adjusted relative risk for bevacizumab compared to ranibizumab was 1.06, 95% CI (0.84, 1.35). The adjusted relative risk differs little from the unadjusted relative risk of 1.08. When the aggregate data from MANTA was included in the adjusted analysis, the relative risk was 1.09, 95% CI (0.89,1.35). The adjusted relative risk for death was 0.99, 95% CI (0.69, 1.43) (Figure 2 available at http://www.aaojournal.org). When the aggregate data from MANTA was included in the adjusted analysis, the relative risk was 1.01, 95% CI (0.71,1.45). Estimated risk for APTC arteriothrombotic events was lower for bevacizumab (0.89) but with the 95% confidence interval spanning (0.62, 1.28) (Figure 3 available at http://www.aaojournal.org). The adjusted relative risks for systemic SAEs related to anti-VEGF treatment and those not related to anti-VEGF treatment were nearly identical (1.10 and 1.11, respectively) (Figures 4, 5 available at http://www.aaojournal.org). There were too few gastrointestinal hemorrhages reported (1 for ranibizumab in GEFAL, 1 for ranibizumab in LUCAS) to add any meaningful information to the imbalance reported in CATT (7 for bevacizumab, 2 for ranibizumab).

The percentage of the variability in relative risks due to heterogeneity across studies, rather than to sampling error, is given by the I^2 statistic in each of the Figures. Heterogeneity was moderate for the proportion of patients with 1 or more systemic SAE (50%) and systemic SAEs

not related to systemic anti-VEGF treatments (59%), substantially less (30%) for arteriothrombotic events, and 0% for death and events related to systemic anti-VEGF treatment.

DISCUSSION

The individual patient data meta-analyses yielded no significant differences in risk of systemic SAEs between bevacizumab and ranibizumab. Thus, while the point estimate for relative risk indicated an approximate 10% increase with bevacizumab relative to ranibizumab for most categories of SAE, a similar 10% decrease for arteriothrombotic events was found. However, the confidence intervals for the relative risks spanned values, both for increased risk and decreased risk with bevacizumab, that would be clinically important for events such as death, cerebro- and cardio-vascular events, and cancer. The adjusted analyses produced results indicating less risk with bevacizumab than in the unadjusted analyses; however, the reduction was minor.

Now that 10 years have passed since the introduction of bevacizumab and ranibizumab for treatment of neovascular age-related macular degeneration, new head-to-head trials are no longer likely to be performed. Although the recent Cochrane meta-analyses of systemic SAEs and the unadjusted meta-analysis based on aggregated data reported here did not include the same set of trials, they yielded similar relative risks of approximately 1.1 for 1 or more SAEs through 1 or 2 years. A trial in India of 120 patients with no adverse events reported,[28] a trial in the United States of 28 patients with 2 deaths reported in 20 patients treated with bevacizumab (1 meckel cell carcinoma and 1 cause unknown),[29] and a trial in Germany registered on ClinicalTrials.gov but without presentation at a national meeting or in a peer-reviewed journal were included in the meta-analysis by Moja but not the current one.[30] Moja noted that, in a personal communication, the German researchers reported SAEs in 21% (22/107) of patients treated with bevacizumab and in 11% (6/54) of patients treated with ranibizumab.[15] Because

small imbalances on strong risk factors such as age, smoking history, hypertension, diabetes, and aspirin and anti-coagulant use can result in biased estimates of difference in risk, this review was initiated to find out whether such imbalances might have influenced the result of meta-analyses that used aggregate data from the clinical trials.

There are some weaknesses in this meta-analysis. First, all the trials were of modest size (<1200 patients each). Second, although there was a common definition of an SAE across trials, the methods of ascertaining the occurrence of an SAE may have varied among trials. Third, the dosing intervals varied across the trials. Comparisons between the drugs were made within each dosing regimen, but the monthly, as needed, and treat and extend approaches were used among the trials. Fourth, individual patient data could not be obtained for one of the clinical trials and only a secondary analysis using aggregate data from that trial could be performed. Fifth, there was moderate heterogeneity across the 5 trials in the proportion of patients with 1 or more systemic SAE and systemic SAEs not related to systemic anti-VEGF treatments, due mainly to results from LUCAS. We attribute this to random variation because eligibility, dose, and visual acuity results in LUCAS were similar to those in the other trials and the ascertainment of SAEs was made by staff masked to study drug. In addition to the strength of the study of being able to account for possible imbalances in prognostic factors through use of patient-level data, the present study employed survival analysis methods that incorporate not only the occurrence of an SAE but also the time since initiation of treatment, thus providing a more precise assessment of differential risk than simply comparing the cumulative numbers at either 1 or 2 years of follow-up.

The meta-analyses on individual patient data in this review, as well as previous meta-analyses on aggregate data, support the conclusion that large differences between bevacizumab and ranibizumab in risk of systemic serious adverse events; i.e., relative risks of ≥1.5, are unlikely. Although the estimated relative risks indicate an approximate 10% increase

for most types of SAEs and a 10% decrease in arteriothrombotic events for bevacizumab, these point estimates have confidence intervals that include up to a 50% increase or decrease in risk. In the absence of additional large-scale clinical trials, further investigation of the differential risk of these anti-VEGF agents can be carried out only though epidemiologic surveillance using administrative or healthcare databases.

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FIGURE LEGEND

Figure 1. Forest Plot for the Adjusted Relative Risk for 1 or More Systemic Serious Adverse Events for Bevacizumab Compared to Ranibizumab.

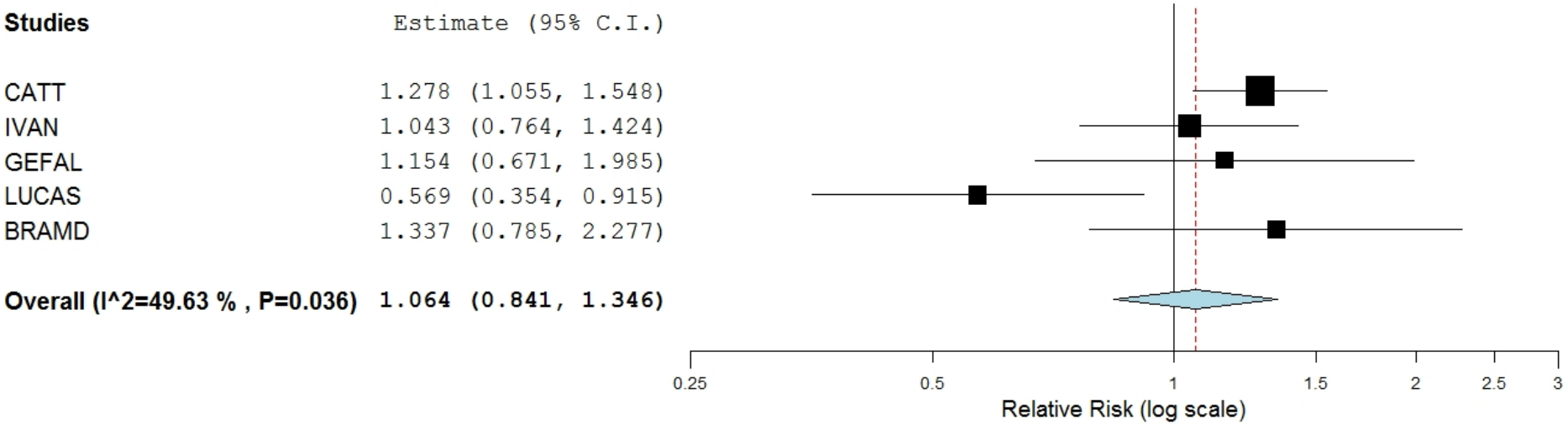
Studies
Estimate (95% C.I.)
CATT 1.278 (1.055, 1.548)
IVAN 1.043 (0.764, 1.424)
GEFAL 1.154 (0.671, 1.985)
LUCAS 0.569 (0.354, 0.915)
BRAMD 1.337 (0.785, 2.277)
Overall (I^2=49.63 % , P=0.036) 1.064 (0.841, 1.346)
0.25
0.5
1
1.5
2
2.5
3
Relative Risk (log scale)

Figure 2. (Supplementary) Forest Plot for the Adjusted Relative Risk for Death for Bevacizumab Compared to Ranibizumab

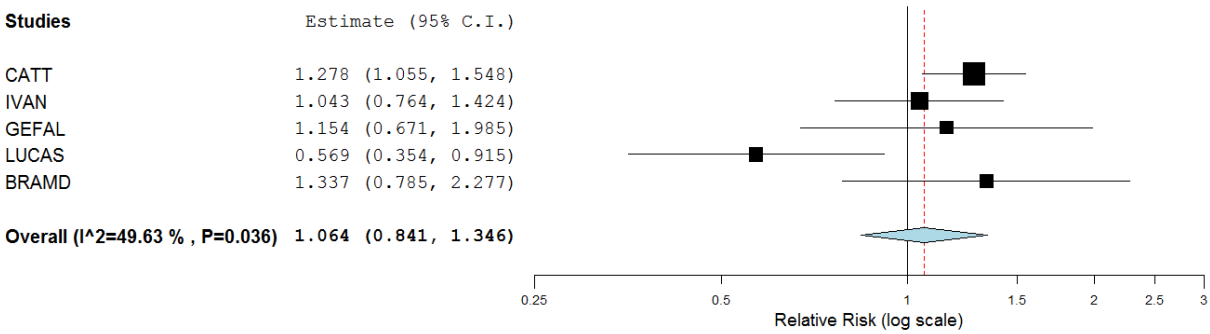

Figure 3. (Supplementary) Forest Plot for the Adjusted Relative Risk for Antiplatelet Trialists' Collaboration (APTC) Arteriothrombotic Event as for Bevacizumab Compared to Ranibizumab

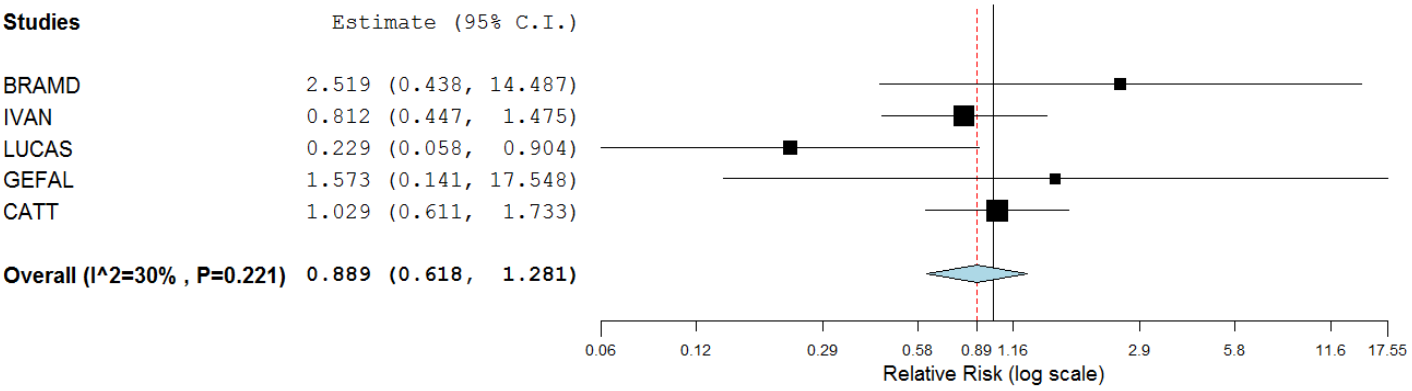

Figure 4. (Supplementary) Forest Plot for the Adjusted Relative Risk for Events Related to Anti-VEGF Treatment for Bevacizumab Compared to Ranibizumab

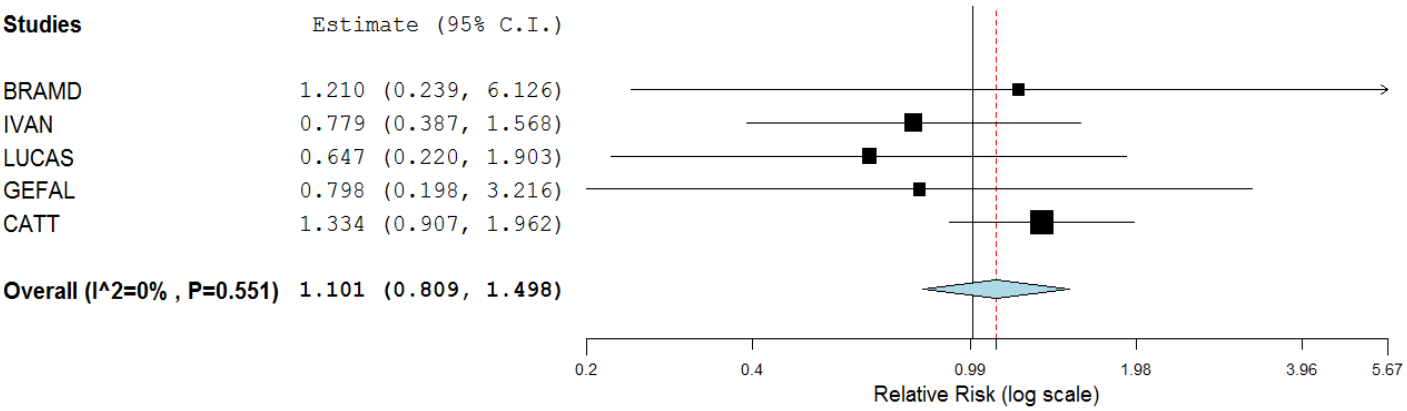

Figure 5. (Supplementary) Forest Plot for the Adjusted Relative Risk for Events Not Related to Anti-VEGF Treatment for Bevacizumab Compared to Ranibizumab

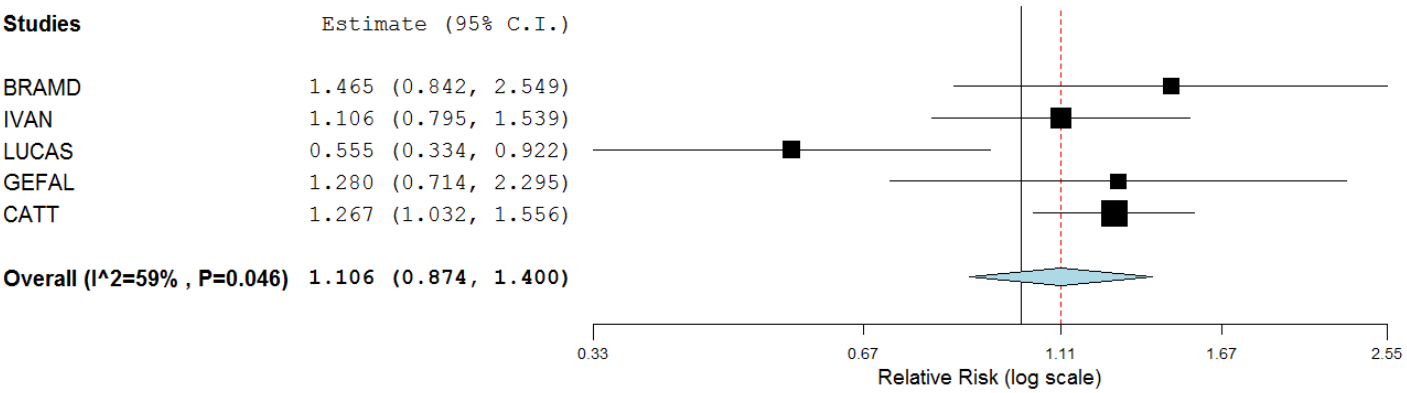

Table 1. Distribution of Baseline Characteristics Available from Each Clinical Trial by Drug

	Clinical Trial					
Characteristic	**CATT**	**IVAN**	**GEFAL**	**LUCAS**	**BRAMD**	**Overall**
Drug, N						
Bevacizumab	586	296	246	220	165	1513
Ranibizumab	599	314	239	221	166	1539
Age (yrs), mean						
Bevacizumab	79.7	77.7	79.5	78.6	77.1	78.8
Ranibizumab	78.8	77.8	79.0	78.0	77.0	78.3
Female (%)						
Bevacizumab	62.1	61.2	62.2	70.6	55.2	62.4
Ranibizumab	61.4	58.9	70.3	64.2	55.4	62.0
Current or past smoker (%)						
Bevacizumab	57.7	62.5	NA	55.5	54.6	58.0
Ranibizumab	56.8	63.7	NA	52.0	51.8	57.0
Diabetic (%)						
Bevacizumab	18.3	9.1	11.8	7.0	10.9	13.0
Ranibizumab	16.7	11.8	10.9	6.4	12.7	12.9
Hypertension (%)						
Bevacizumab	70.3	61.2	61.8	57.9	57.0	63.9
Ranibizumab	68.6	59.9	53.1	53.2	66.9	62.0
Aspirin (%)						
Bevacizumab	50.9	31.4	NA	29.0	NA	41.3
Ranibizumab	45.9	27.1	NA	30.3	NA	37.7
Anticoagulant (%)						
Bevacizumab	16.6	4.4	NA	7.7	NA	11.5
Ranibizumab	17.7	6.1	NA	9.1	NA	12.8

NA = Not available.

Table 2. Systemic Serious Event and its Type from Each Clinical Trial by Drug

Characteristic	CATT	IVAN	GEFAL	LUCAS	BRAMD	Total
N						
Bevacizumab	586	296	246	220	165	1513
Ranibizumab	599	314	239	221	166	1539
≥1 SAE: n (%)						
Bevacizumab	234 (39.9%)	80 (27.0%)	30 (12.2%)	29 (13.2%)	30 (18.2%)	403 (26.6%)
Ranibizumab	190 (31.7%)	81 (25.8%)	24 (10.0%)	45 (20.4%)	26 (15.7%)	366 (23.8%)
Death: n (%)						
Bevacizumab	36 (6.1%)	15 (5.1%)	2 (0.8%)	4 (1.8%)	1 (0.6%)	58 (3.8%)
Ranibizumab	32 (5.3%)	15 (4.8%)	3 (1.3%)	7 (3.2%)	1 (0.6%)	58 (3.8%)
APTC: n (%)						
Bevacizumab	29 (4.9%)	20 (6.8%)	2 (0.8%)	3 (1.4%)	4 (2.4%)	58 (3.8%)
Ranibizumab	28 (4.7%)	25 (8.0%)	1 (0.4%)	9 (4.1%)	2 (0.9%)	65 (4.2%)
VEGF-related: n (%)						
Bevacizumab	62 (10.6%)	14 (4.7%)	4 (1.6%)	6 (2.7%)	3 (1.8%)	89 (5.9%)
Ranibizumab	45 (7.5%)	19 (6.1%)	4 (1.7%)	8 (3.6%)	3 (1.8%)	79 (5.1%)
Not VEGF-related: n (%)						
Bevacizumab	202 (34.4%)	73 (24.7%)	27 (11.0%)	25 (11.4%)	29 (17.6%)	356 (23.5%)
Ranibizumab	170 (28.4%)	70 (22.2%)	20 (8.4%)	40 (18.1%)	23 (13.9%)	323 (21.0%)

NA is not available.

APTC = Antiplatelet Trialists' Collaboration arteriothrombotic events

VEGF is vascular endothelial growth factor

Table 3. Summary of Estimated Relative Risks of Systemic Serious Adverse Events after Treatment with Bevacizumab Compared to Ranibizumab

Systemic Serious Event Type	Bevacizumab (N=1513) With Event n (%)	Ranibizumab (N=1539) With Event n. (%)	Relative Risk (95% CI) Unadjusted	Relative Risk (95% CI) Adjusted	P-value Adjusted Model
≥1 event	403 (26.6%)	366 (23.8%)	1.08 (0.90,1.30)	1.06 (0.84,1.35)	0.61
Death	58 (3.8%)	58 (3.8%)	1.03 (0.72,1.48)	0.99 (0.69,1.43)	0.97
APTC	58 (3.8%)	65 (4.2%)	0.93 (0.66,1.32)	0.89 (0.62,1.28)	0.53
VEGF-related	89 (5.9%)	79 (5.1%)	1.16 (0.86,1.56)	1.10 (0.81,1.50)	0.54
Not VEGF-related	356 (23.5%)	323 (21.0%)	1.14 (1.00,1.30)	1.11 (0.87,1.40)	0.40

APTC is Antiplatelet Trialists' Collaboration arteriothrombotic events
VEGF is vascular endothelial growth factor

Precis

A meta-analysis on individual patient data supports the conclusion that large differences between bevacizumab and ranibizumab in risk of systemic serious adverse events; i.e., relative risks of ≥1.5, are unlikely.

Credit Roster for the Bevacizumab-Ranibizumab International Trials Group

Credit Roster for the BRAMD

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Credit Roster for Comparison of AMD Treatments Trials (CATT)

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