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Original Article

Comparing bevacizumab and ranibizumab for treatment of neovascular age-related macular degeneration: a meta-analysis of noninferiority randomized controlled trials

Xiaotang Wang[1*], Dan Qin[1*], Yong Liu[2], Runjia Lei[3], Meixia Ren[4], Runsheng Wang[4], Ying Wang[1]

[1]Department of Ophthalmology, Honghui Hospital, Xi'an Jiaotong University, Xi'an City 710054, Shaanxi Province, P.R. China; [2]Department of Neurosurgery, Tangdu Hospital, Fourth Military Medical University, Xi'an City 710038, Shaanxi Province, P.R. China; [3]Department of Ophthalmology, Xi'an NO.1 Hospital, Xi'an City 710002, Shaanxi Province, P.R. China; [4]Department of Ophthalmology, Xi'an NO.4 Hospital, Xi'an City 710004, Shaanxi Province, P.R. China. [*]Equal contributors.

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Abstract: Neovascular age-related macular degeneration (nAMD) is the main cause of blindness in populations aged over 50 years old. The objective of this meta-analysis was to compare the efficacy and safety of off-label use of bevacizumab with licensed ranibizumab for the treatment of nAMD. Five noninferiority randomized controlled trials (RCTs) comparing bevacizumab with ranibizumab for treatment of nAMD were included. Three reviewers independently extracted data. Data on efficacy and safety outcomes were collected. Pooled risk ratios, weighted mean difference (WMD), and associated 95% confidence interval (CI) were calculated. There were 1,346 patients in the bevacizumab group and 1,392 patients in the ranibizumab group. There were no significant differences between the two drugs in the change of BCVA (WMD=-0.63; 95% CI, -1.72 to 0.46, P=0.26). The mean difference was -0.63 letters with a lower limit in the 95% CI of -1.72 letters. This lower bound was above all the noninferiority margins chosen in the RCTs (-3.5 to -5). Bevacizumab was more effective in reducing central retinal thickness than ranibizumab (WMD=11.14; 95% CI, 2.12 to 20.15, P=0.02). The pooled risk ratios comparing the incidences of death, arteriothrombotic events, venous thrombotic events, ≥ 1 serious systemic events, and ocular adverse events were not statistically different. The pooled evidence confirmed that bevacizumab is non-inferior to ranibizumab for treatment of nAMD. However, bevacizumab tended to have better anatomical outcome. There was no difference in adverse events between the two drugs. Further trials are still needed to strengthen results because of the limited number of studies.

Keywords: Neovascular age-related macular degeneration, bevacizumab, ranibizumab, meta-analysis

Introduction

Neovascular age-related macular degeneration (nAMD) is a chronic, progressive disease of the retina and a leading cause of irreversible loss of central vision in populations older than 50 years old [1]. Vascular endothelial growth factor-A (VEGF-A) plays a major role in nAMD pathogenesis [2]. The anti-VEGF drugs ranibizumab and bevacizumab are highly effective treatments for nAMD and preserve visual acuity [3, 4].

Ranibizumab (Lucentis®) is a recombinant, fully humanized, affinity-matured monoclonal antigen-binding antibody fragment that inhibits receptor-binding of multiple biologically active forms of VEGF-A [5]. Ranibizumab has been widely used as treatment of nAMD since approved by the U.S. Food and Drug Administration in 2006 [6-8].

Bevacizumab (Avastin®) has a similar chemical structure and mechanism of action to ranibizumab [9]. However, a significant advantage of bevacizumab is that it is less expensive than ranibizumab [10]. Reports have suggested that the US Medicare system could save more than one billion dollars within two years if ranibizumab was replaced by bevacizumab [11]. Bevacizumab has been used as an off-label treatment for nAMD with encouraging results and lower cost [12-14].

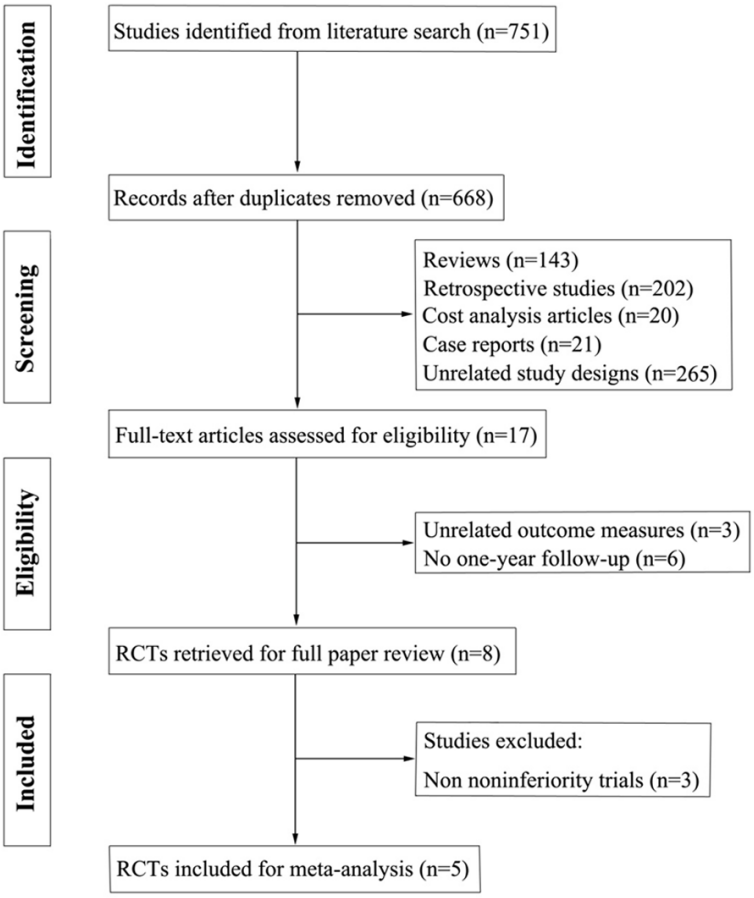

Figure 1. Flowchart of literatures screening.

There have been multiple, large muliticenter randomized controlled trials (RCTs) assessing the relative efficacy and safety of bevacizumab and ranibizumab for treatment of nAMD [3, 15-18]. To determine whether intravitreal injection of bevacizumab is non-inferior to ranibizumab, we performed a meta-analysis of pooled evidence from noninferiority RCTs.

Materials and methods

Search strategy

The systematic search was performed on PubMed, EMBASE, the Cochrane Library, and clinicaltrials.gov from inception of the study until August 2017, using relevant text words and medical subject headings that included all spellings of "*neovascular age-related macular degeneration or nAMD*", "*bevacizumab or BEV or Avastin*", "*ranibizumab or RAN or Lucentis*". Publication language was restricted to English. Trial registers were also checked for unpublished studies and a manual search was performed by checking the reference lists of original reports and review articles identified by the electronic search for other potentially eligible articles.

Eligibility criteria for considering studies

To be considered eligible for inclusion in this meta-analysis, the studies had to meet the following criteria: 1) study design-noninferiority RCT; 2) patients-previously untreated nAMD; 3) intervention-bevacizumab versus ranibizumab; 4) primary outcomes-best corrected visual acuity (BCVA); 5) follow-up time-one year. Abstracts from full texts and conferences without raw data available for retrieval, duplicate publications, letters, and reviews were excluded. When sequential reports were on the same cohort of patients, the most recent report was included. Data that could not be obtained from the last publication were obtained from previous reports.

Outcomes

For efficacy, the primary outcome was the mean change in BCVA between bevacizumab and ranibizumab from baseline at one year. Treatment response in BCVA from baseline was divided into four types as follows: responders, defined as the proportion of patients with a loss of BCVA less than 15 letters; stabilizers, defined as the proportion of patients with a loss or a gain of BCVA less than 15 letters; losers, defined as the proportion of patients with 15 letters loss or more of BCVA; gainers, defined as the proportion of patients with 15 letters gain or more of BCVA [15]. Secondary outcome measures were the mean change in central retinal thickness (CRT), area of lesion, and number of injections from baseline at one year. Safety was also analyzed by comparing the incidence of adverse events based on the

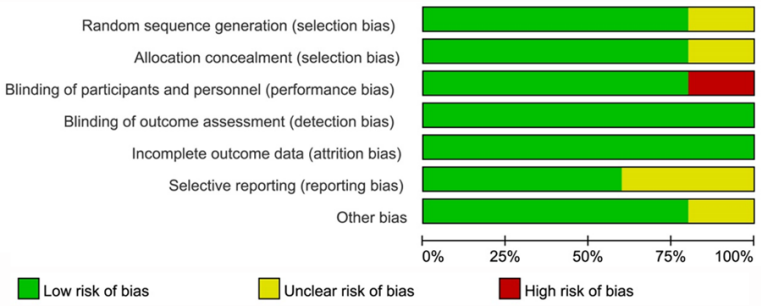

Figure 2. Risk of bias graph.

Medical Dictionary for Regulatory Activities (MedDRA) system organ class including death, arteriothrombotic events, venous thrombotic events, ≥ 1 serious systemic adverse events, and ocular adverse events [19].

Data extraction

The data were extracted independently by three reviewers. Disagreement was resolved by discussion. The information extracted from each study included the authors, the year of publication, study design, country in which the trial was conducted, noninferiority limit, number of patients, the mean change in BCVA measured as Early Treatment Diabetic Retinopathy Study letters, mean change in CRT, and the incidence of death, arteriothrombotic events, venous thrombotic events, ≥ 1 serious systemic events, and ocular adverse events.

Qualitative assessment

Qualities of the included RCTs were assessed by three independent observers using the Jadad score and the risk of bias assessment [20, 21]. In Jadad scoring, the scale consists of three items describing randomization (0-2 points), blinding (0-2 points), and dropouts and withdrawals (0-1 points). The total score ranges from 0 to 5 points, and the studies with a score ≥ 3 points were considered high quality. In the assessment of risk of bias, the following key domains were assessed: randomization sequence generation, allocation concealment, masking or blinding of participants, trial personnel, and outcome assessors in terms of treatment regimen, incomplete outcome data, selective outcome reporting (i.e., absence of data for outcome measurements), and other biases (i.e., bias due to problems not covered elsewhere). For the domains above, each parameter was judged as low, high, or unclear/unknown risk of bias.

Statistical analysis

Quantitative data were entered into the Cochrane Review Manager (RevMan, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark). For continuous variables (i.e., BCVA and CRT), the weighted mean difference (WMD) was measured. The risk ratios (RR) were measured for dichotomous variables such as adverse events. All of the outcomes are reported with a 95% confidence interval (CI). $P < 0.05$ was considered statistically significant. Chi-square and I^2 were calculated to assess heterogeneity between studies. $P < 0.05$, and $I^2 \geq 50\%$ were considered representative of significant statistical heterogeneity [22]. If there was heterogeneity between studies, a random-effects model was applied. Alternatively, a fixed-effects model was used for pooling the data.

Results

Overall characteristics of selected trials

A total of 751 articles were initially identified and 746 were rejected according to the exclusion criteria. The five remaining full-text articles that met inclusion criteria were included in this meta-analysis [3, 15-18]. The flow diagram of search results is shown in **Figure 1**. In total, there were 2,738 patients included in this meta-analysis with 1,346 patients in the bevacizumab group and 1,392 patients in the ranibizumab group. All trials were multicenter and one trial (CATT [3]) was conducted in America and the other trials (LUCAS [18], IVAN [17], GEFAL [16], and BRAMD [15]) were conducted in Europe. The main characteristics of the five trials included in the meta-analysis are shown in **Tables 1** and **2**.

Quality assessment

Based on Jadad scoring, all RCTs included in our meta-analysis were considered high quality. The risk of bias summary and graphs for each trial are presented in **Figures 2** and **3**.

Table 1. Summary of the characteristics of the included RCTs

Study (year, country)	Study design	Noninferi-ority limit (letters)	Intervention (intravitreal injection)	Follow-up (m)	Per protocol BEV/RAN	Primary outcome	Secondary outcomes	Jadad score
LUCAS [18] (2015 NOR)	Multicenter Noninferiority RCTs	5	RAN 0.5 mg, BEV 1.25 mg, PRN	12	184/187	BCVA	No. of injections, CRT, AOL, AEs	5
CATT [3] (2011 USA)	Multicenter single-blind Noninferiority RCTs	5	RAN 0.5 mg, BEV 1.25 mg, monthly + PRN	12	536/569	BCVA	No. of injections, CRT, AOL, cost, AEs	4
IVAN [17] (2012 UK)	Multicenter factorial Noninferiority RCTs	3.5	RAN 0.5 mg, BEV 1.25 mg, monthly + PRN	12	274/287	BCVA	No. of injections, CRT, AOL, contrast sensitivity and reading index, cost, near visual acuity, serum VEGF level, AEs	4
GEFAL [16] (2013 FRA)	Multicenter prospective Double-masked Noninferiority RCTs	5	RAN 0.5 mg, BEV 1.25 mg, monthly + PRN	12	191/183	BCVA	No. of injections, CRT, AOL, AEs	5
BRAMD [15] (2016 NL)	Multicentre Double-masked Noninferiority RCTs	4	RAN 0.5 mg, BEV 1.25 mg, monthly	12	161/166	BCVA	CRT, AOL, AEs	3

PRN-pro re nata, BEV-bevacizumab, RAN-ranibizumab, BCVA-best corrected visual acuity, CRT-central retinal thickness, AOL-area of lesion, AEs-adverse events.

Table 2. Outcomes at final evaluation of each RCTs

Study (year, country)	Age (m±SD, y)	Sex (F, %)	Change of BCVA from baseline (m±SD, letters)	Change of CRT from baseline (m±SD, μm)	Change of area of lesion from baseline (m±SD, mm2)	No. of injections (m±SD)	Adverse events				
							Death (n, %)	AT (n, %)	VT (n, %)	≥ 1 SSE (n, %)	Ocular (n, %)
LUCAS[18] (2015 NOR)	B78.7±7.6 R78.0±8.2	B151 (70.9) R140 (64.2)	B7.9±13.4 R8.2±12.5	B-112.0±105.0 R-120.0± 97.0	B-1.3±4.1 R-1.0±3.5	B8.9±2.6 R8.0±2.3	B4 (1.8) R7 (3.2)	B3 (1.4) R10 (4.5)	B0 (0.0) R2 (0.9)	B37 (16.8) R45 (20.4)	B5 (2.3) R0 (0.0)
CATT[3] (2011 USA)	B79.7±7.5 R78.8±7.6	B364(62.1) R368(61.4)	B6.9±15.8 R7.6±13.6	B-79.0±127.4 R-90.5±132.2	B0.3±2.3 R0.0±0.1	B9.8±3.4 R9.3±3.4	B15 (2.6) R9 (1.5)	B14 (2.4) R13 (2.2)	B5 (0.9) R2 (0.3)	B141 (24.1) R114 (19.0)	B4 (0.7) R3 (0.5)
IVAN[17] (2012 UK)	B77.7±7.2 R77.8±7.6	B181(61.1) R185(58.9)	B5.0±16.7 R7.2±15.9	B-84.0±121.3 R-99.0±118.5	B-3.5±5.0 R-2.9±4.6	B11.0±8.9 R10.0±8.9	B5 (1.7) R6 (2.0)	B1 (0.3) R6 (1.9)	B2 (0.7) R0 (0.0)	B37 (12.5) R30 (9.6)	NR
GEFAL[16] (2013 FRA)	B79.6±6.9 R78.7±7.3	B119(62.3) R129(70.5)	B4.8±14.9 R2.9±15.1	B-95.0±132.8 R-107.2±103.3	B-0.3±1.5 R-0.3±1.4	B6.8±2.7 R6.5±2.4	B2 (0.8) R3 (1.2)	B1 (0.4) R1 (0.4)	B1 (0.4) R0 (0.0)	B30 (12.2) R24 (10.0)	B2 (0.8) R5 (2.1)
BRAMD[15] (2016 NL)	B79.0±7.0 R78.0±7.0	B89(55.2) R93(56.0)	B5.1±14.1 R6.4±12.2	B-131.0±129.0 R-138.0±117.0	NR	NR	B1 (0.6) R1 (0.6)	NR	NR	B34 (21.1) R37 (22.3)	NR

B-bevacizumab, R-ranibizumab, BCVA-best corrected visual acuity, CRT-central retinal thickness, NR-no reported, AT-arteriothrombotic events, VT-venous thrombotic events, SSE-serious systemic events.

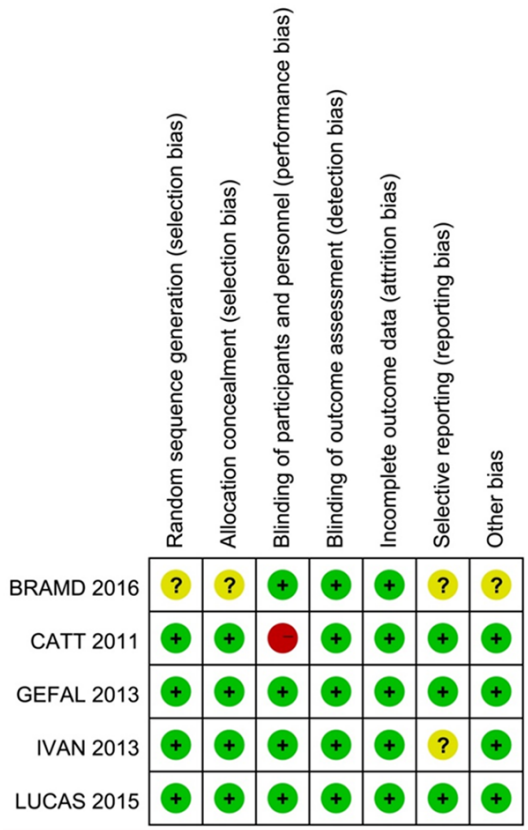

Figure 3. Risk of bias summary.

Selection bias, allocation concealment, and other biases were appropriate in four trials with low risk whereas only the trial of BRAMD [15] was unclear. Participants and personnel of all trials were blinded except for the trial of CATT [3]. The blinding of outcome assessment and missing data were low risk in all trials. Selective reporting in IVAN [17] and BRAMD [15] were unclear and other trials were low risk.

Efficacy analysis

Pooled WMD of changes in BCVA between the two drugs at one year are shown in **Figure 4**. As the functional outcome, BCVA improved in both drugs. Although ranibizumab tended to have more BCVA improvement, the difference was not significant (WMD=-0.63; 95% CI, -1.72 to 0.46, P=0.26), with no heterogeneity identified (I^2=6%, P=0.37). Ranibizumab had a higher proportion of BCVA responders, but the difference was not significant (WMD=0.98; 95% CI, 0.96 to 1.00, P=0.11). Similarly, although not statistically significant, ranibizumab had a lower proportion of patients with diminished BCVA (WMD=1.32; 95% CI, 0.96 to 1.81, P=0.09). The proportion of BCVA gainers and stabilizers between the two drugs were not statistically different. The treatment responses of both drugs are shown in **Figure 5**.

CRT decreased more significantly in the bevacizumab group after one year than ranibizumab (WMD=11.14; 95% CI, 2.12 to 20.15, P=0.02; **Figure 6A**). Although not statistically different, there was a greater reduction of area of lesion in patients treated with ranibizumab than those receiving bevacizumab (WMD=0.05; 95% CI, -0.14 to 0.23, P=0.62; **Figure 6B**). No statistical heterogeneity was observed in the outcomes of CRT (I^2=0%, P=0.99) and area of lesion (I^2=29%, P=0.24). Additionally, fewer injections were given for ranibizumab than bevacizumab (WMD=0.58; 95% CI, 0.30 to 0.85, P<0.0001) with no statistical heterogeneity (I^2=5%, P=0.37; **Figure 7**).

Safety analysis

Adverse events associated with bevacizumab or ranibizumab treatment and the analysis of the RR and overall effect are shown in **Figure 8**. With the exception of ocular adverse events, no statistical heterogeneity was observed among the trials. There were no significant differences between both drugs with respect to the incidence of death and ocular adverse events (**Figure 8A** and **8E**). Although bevacizumab was associated with a higher frequency of ≥ 1 serious systemic events and venous thrombotic events compared with ranibizumab, the difference was not statistically significant (**Figure 8B** and **8D**). A higher frequency of arteriothrombotic events was observed in the ranibizumab group, but the difference was not statistically significant (**Figure 8C**).

Sensitivity analysis

The robustness of the analysis was assessed by performing sensitivity analyses excluding the CATT study (largest trial). Excluding this study did not alter the results obtained in the previous analysis.

Discussion

The meta-analysis reported here reviewed five noninferiority RCTs including 1,346 patients in the bevacizumab group and 1,392 patients in

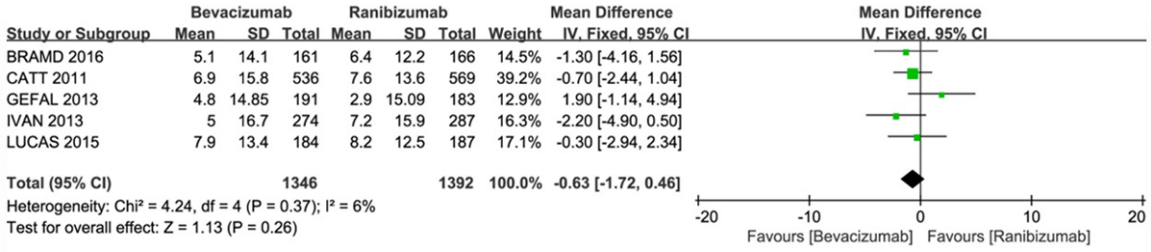

Figure 4. Comparing bevacizumab with ranibizumab for mean change in BCVA from baseline at one year.

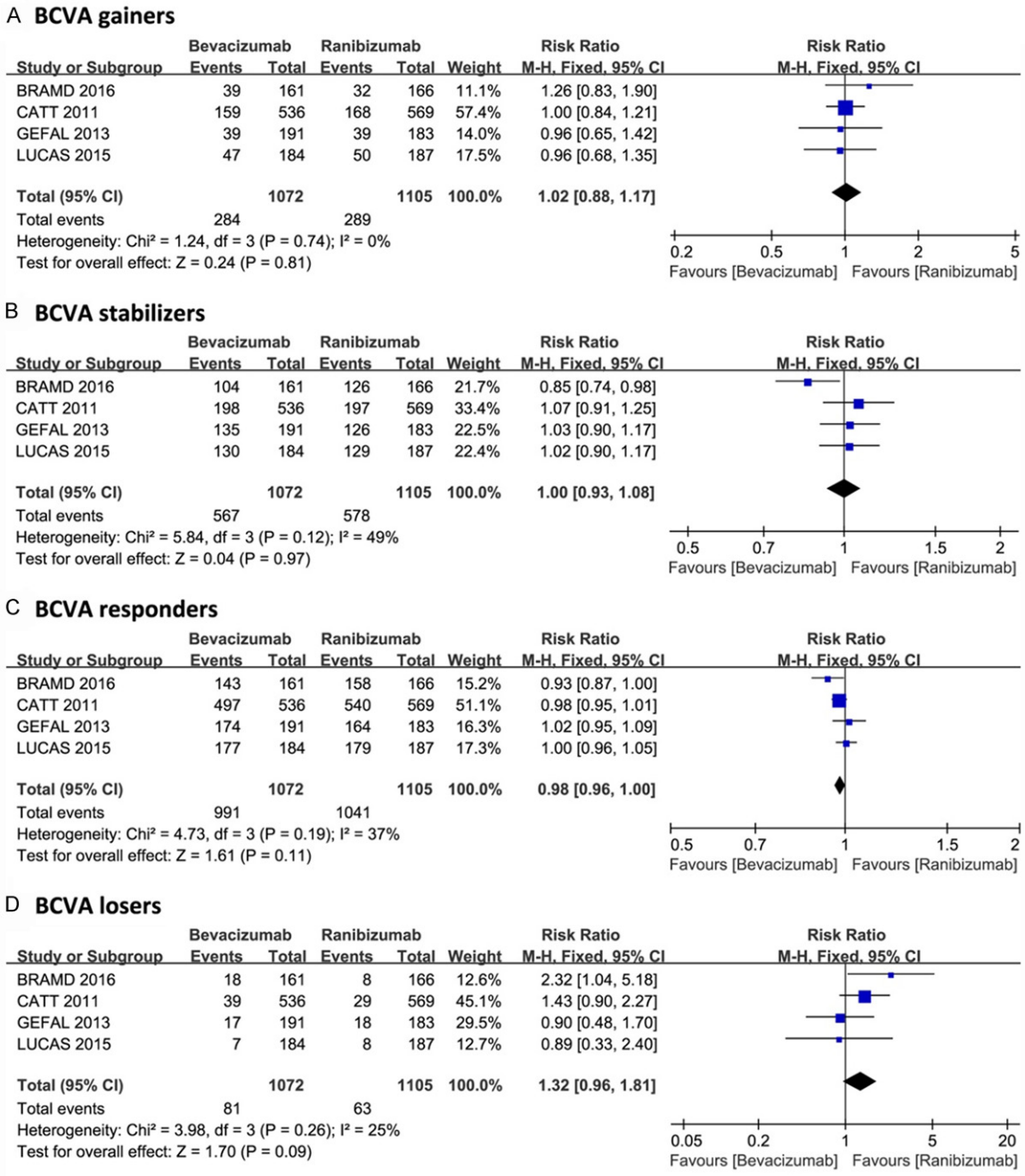

Figure 5. Treatment responses in BCVA comparing bevacizumab with ranibizumab from baseline at one year.

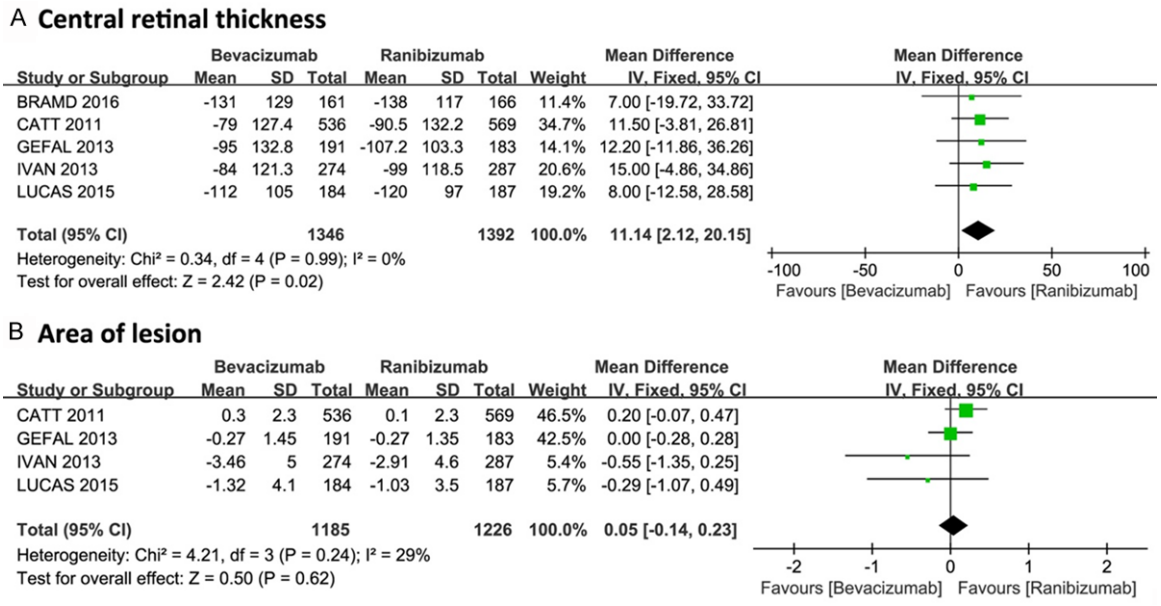

Figure 6. Anatomical outcomes comparing bevacizumab with ranibizumab from baseline at one year.

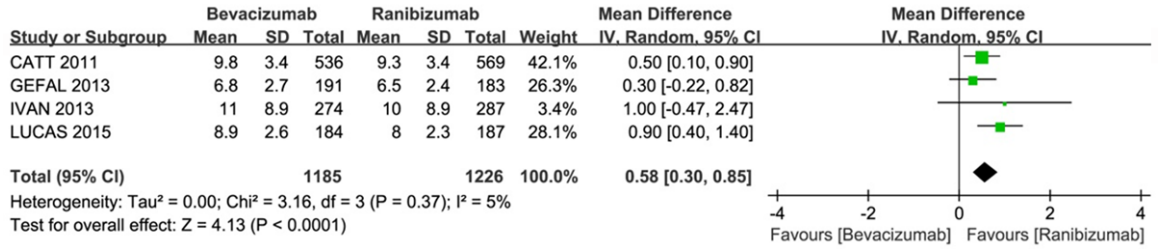

Figure 7. Number of injections comparing bevacizumab with ranibizumab at one year.

the ranibizumab group. This meta-analysis differed from previous studies which analyzed all RCTs [23, 24]. Only noninferiority RCTs were included in our analysis to evaluate whether bevacizumab was equivalent or superior to ranibizumab.

As the functional outcome, there was no difference in the mean change in BCVA between bevacizumab and ranibizumab. The mean difference was -0.63 letters with a lower limit in the 95% CI of -1.72 letters. This lower bound is above all the noninferiority margins chosen in the RCTs (-3.5 to -5). The ranibizumab group had more BCVA responders than bevacizumab, but the difference was not significant. These results suggest functional noninferiority of bevacizumab over ranibizumab for the treatment of nAMD at one year.

In the anatomical outcomes, bevacizumab was more effective in reducing CRT than ranibizumab. In addition, the reduction in area of lesion between both groups was not statistically different. Therefore, bevacizumab demonstrated better improvement in anatomical outcomes compared with ranibizumab. There was more likely to be no absolute correlation between visual function outcome and anatomic outcomes [25, 26].

In the safety profiles, the combined results showed no significant difference in adverse events of both drugs. Serious systemic events were likely to be of higher frequency with bevacizumab compared with ranibizumab, but these differences were not statistically significant, which is inconsistent with a previous study [23]. The meta-analysis by Chen et al. included four RCTs with three non-inferior trials while five non-inferior RCTs were analyzed in our study. Therefore, our findings may be more convincing.

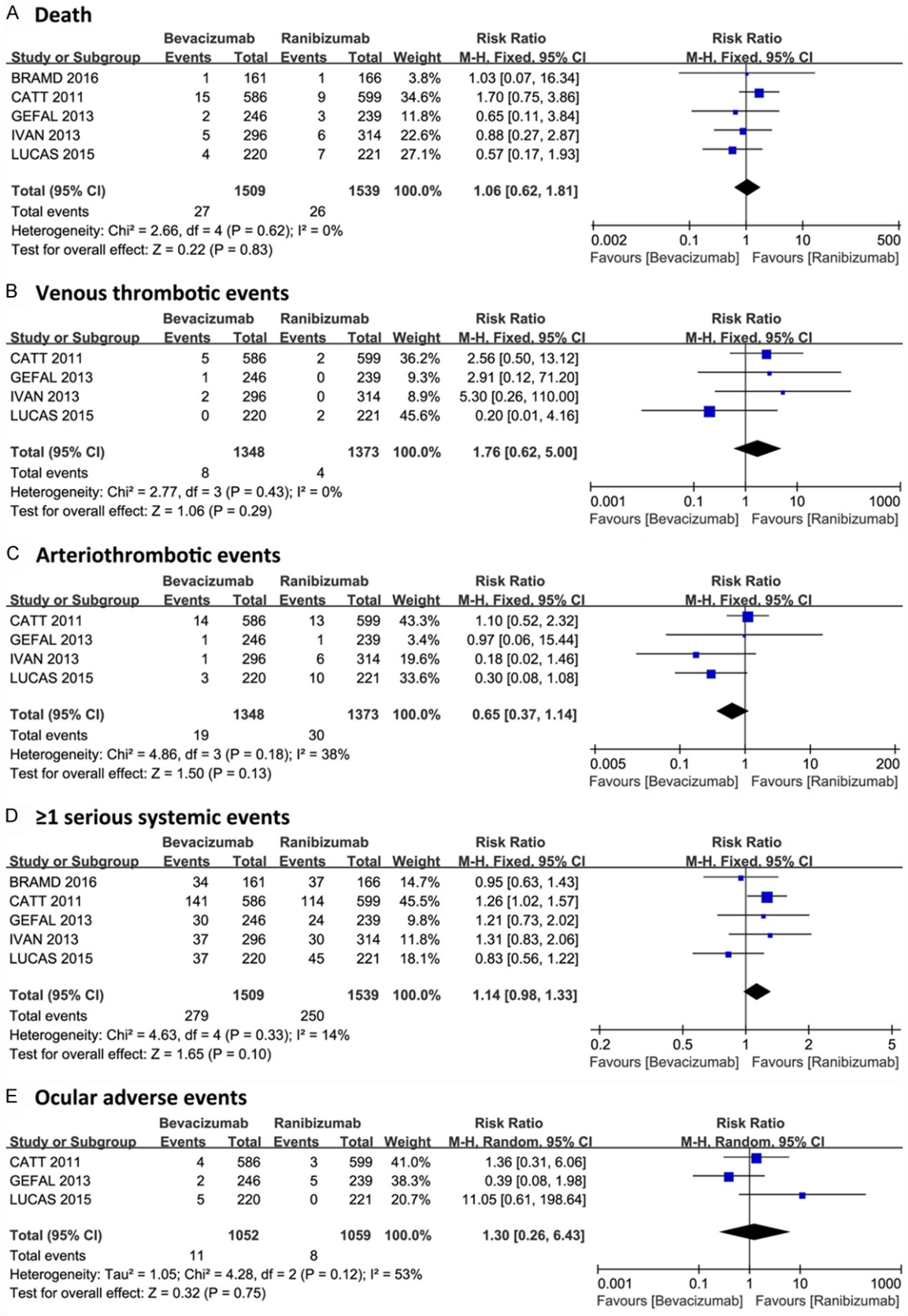

Figure 8. Adverse events comparing bevacizumab with ranibizumab at one year.

This meta-analysis has some limitations. First, a potential source of heterogeneity is severity of nAMD in each trial and lack of data reported in all phases of follow-up. Second, publication bias cannot be fully excluded. Although the sensitivity analysis demonstrated no evidence of publication bias, the results should be interpreted with caution.

In conclusion, this meta-analysis is the most comprehensive review of literature assessing the relative efficacy and safety of bevacizumab and ranibizumab in nAMD. Our findings indicate that bevacizumab and ranibizumab offer equivalent benefit in terms of stabilizing or improving BCVA. Administration of bevacizumab results in significantly better anatomical outcomes and there were no differences between the two drugs in terms of rates of adverse events. Due to the limited number of available studies, further trials are still needed to strengthen our results.

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Disclosure of conflict of interest

None.

Address correspondence to: Ying Wang, Department of Ophthalmology, Honghui Hospital, Xi'an Jiaotong University, 555 Youyi East Road, Beilin District, Xi'an 710054, Shaanxi Province, China. Tel: 86-1804952-2995; E-mail: liu868yong@163.com

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