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Comparison of bevacizumab and ranibizumab in age-related macular degeneration: a systematic review and meta-analysis

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Abstract

• AIM: To compare the effectiveness and safety between bevacizumab and ranibizumab in the treatment of age-related macular degeneration (AMD) through a systematic review and meta-analysis.

• METHODS: We performed a comprehensive search of randomized controlled trials (RCTs), non-RCTs, case-control and cohort studies that compared bevacizumab and ranibizumab using PubMed and the Cochrane Library. After the related data were extracted by two investigators independently, pooled weighted mean differences (WMDs) and risk ratios (RRs) with 95% confidence intervals (CIs) were estimated using a random-effects or a fixed-effects model.

• RESULTS: A total of four RCTs involving 1927 patients and eleven retrospective case series involving 2296 patients were included. For the primary outcomes, no significant differences were found between ranibizumab group and bevacizumab group in visual acuity (WMD: -0.04; 95% CI: -0.08 to 0.00; *P*=0.06), best corrected visual acuity (WMD: -0.05; 95%CI: -0.10 to 0.00; *P*=0.05), retina thickness (WMD: -4.69; 95%CI: -13.15 to 3.76; *P*=0.86) and foveal thickness (WMD: 10.91; 95%CI: -14.73 to 36.56; *P*=0.40). The pooled analyses in the evaluation of safety showed that compared to bevacizumab, ranibizumab was associated with decreased risks of ocular inflammation (RR: 0.45; 95% CI: 0.23 to 0.89; *P*=0.02) and venous thrombotic events (RR: 0.27; 95% CI: 0.08 to 0.89; *P*=0.03). However, there were no significant differences observed in deaths (*P*=0.69) and arterial thromboembolic events (*P* =0.71) between the two groups.

• CONCLUSION: With equal clinical efficacy, ranibizumab was found to be associated with less adverse events compared to bevacizumab, indicating that ranibizumab might be a safer management.

• **KEYWORDS:** age-related macular degeneration; bevacizumab; ranibizumab
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INTRODUCTION

Age-related macular degeneration (AMD) is one of the major causes of blindness in developed countries [1-3]. It is the third leading cause of blindness, coming after cataract and glaucoma, accounting for 8.7% of all legal blindness across the world [4]. The number of individuals affected is estimated to be doubled by the year 2030 owing to the longevity of the aged population [5]. Hence, AMD becomes a major public health problem with significant economic and social impact. Population studies indicate that neovascular AMD accounts for two thirds of late AMD cases and 90% of blindness from AMD[6].

Vascular endothelial growth factor (VEGF), which is regulated by hypoxia, promotes angiogenesis, and its role in the pathogenesis of neovascular AMD is well recognized[7,8]. The advent of intravitreous VEGF inhibitors has renovated the management of neovascular AMD. There are various anti-VEGF drugs commonly used nowadays, such as pegaptanib, ranibizumab and bevacizumab [9,10]. The effectiveness of pegaptanib was not as ideal as ranibizumab and bevacizumab, visual decline was still seen in the AMD patients after treatment[11].

Bevacizumab is a humanized anti-VEGF monoclonal IgG_1 antibody [12,13]. In combination with chemotherapy, it was originally approved by the Food and Drug Administration for

the treatment of various cancers, such as colorectal cancer, non-small cell lung cancer and renal cell cancer. The effectiveness of bevacizumab on wet AMD was first shown by Rosenfeld *et al* [14]. Ranibizumab, a recombinant monoclonal antibody fragment that inhibits VEGF, has been approved for the treatment of all angiographic subtypes of subfoveal neovascular AMD by the Food and Drug Administration since 2006 and by the European Medicines Agency since 2007 [15]. The approval was based on two randomized clinical trials (RCTs), in which approximately 95% of the patients treated with monthly ranibizumab injections lost fewer than 15 letters in 12mo, compared to 64% of patients receiving photodynamic therapy (PDT) and 62% receiving sham treatment [16]. The costs of ranibizumab, however, are immense. With monthly injections at a dose of 0.5 mg, the annual costs count up to more than US $23 000 per patient, about 10 times more than that of bevacizumab[17,18]. Although many studies, including large RCTs, tried to compare the efficacy of ranibizumab and bevacizumab for the treatment of AMD, the results were controversial [19]. Therefore, a systematic review and meta-analysis of pooled data from RCTs and non-RCTs were performed in this study, aiming to evaluate the clinical effectiveness of bevacizumab and ranibizumab in the treatment of AMD.

SUBJECTS AND METHODS

Systematic Literature Search The systematic review and meta-analysis considered RCTs and non-RCTs comparing bevacizumab versus ranibizumab for the treatment of patients with AMD. We searched PubMed (1966-October 2012) and the Cochrane Library (1988-October 2012) without language restrictions. Search terms including MeSH words and text words. The terms we used were 'Lucentis' or 'ranibizumab' or 'Avastin' or 'bevacizumab' or 'age-related macular degeneration' or AMD'. Furthermore, we perused the bibliographies of retrieved articles and relevant reviews. If the studies did not contain all of the necessary information, we contacted the authors directly to obtain the missing data.

Inclusion and Exclusion Criteria For inclusion, studies had to meet the following criteria: 1) RCTs or non-RCTs studies, which compared the efficacy or safety between bevacizumab and ranibizumab in patients with AMD. Studies with full data information needed were included in the meta-analysis; 2) at least one of the primary outcomes [*i.e.* visual acuity (VA), best-corrected visual acuity (BCVA), foveal thickness (FT), retina thickness (RT) and central macular thickness (CMT)] or secondary outcomes (serious adverse effects, such as ocular inflammation, deaths and thromboembolic events) were evaluated; 3) enrolled a minimum of 10 eyes. If multiple papers from the same study were identified, only the one with the most detailed information and longest follow-up was selected for inclusion. Studies were excluded if they: 1) included patients with other diseases but not AMD, including choroidal neovascularization, choroid melanoma, drusen, subretinal hemorrhage and diabetic macular retinopathy; 2) evaluated bevacizumab or ranibizumab as monotherapy; 3) had no original data (reviews, comments or letters), and 4) not conducted in humans.

Data Extraction and Quality Assessment To avoid bias in the data extraction process, two investigators (Zhang XY and Guo XF) independently extracted and collected data following the selection criteria described above. Any discrepancy was resolved by discussion and consensus. The following information was extracted from each trial: first author's name, publication year, type of study, the number of treated patients, duration of follow-up, dosage, injections per patient and main findings. An electronic abstraction database was established in Microsoft Excel. We evaluated the quality of the studies included in this research with the Jadad score for RCTs and Newcasle-Ottawa Scale (NOS) for non-RCTs. The range of Jadad score is from 1 to 5 and the range of NOS is from 1 to 9[20,21].

Statistical Analysis To evaluate the efficacy and safety between bevacizumab and ranibizumab for the treatment of AMD, we assessed the overall effect of bevacizumab and ranibizumab from the data of the included studies and used the weighted mean differences (WMDs) and risk ratios (RRs) with 95% confidence intervals (CIs) as the metric of choice for all the outcomes. We implemented meta-analysis of the direct evidence for each outcome, combining pairwise comparisons between bevacizumab and ranibizumab using Review Manager 5.0. Between-study heterogeneity was evaluated by Q-statistic and quantified by the I^2 statistic. If statistically significant heterogeneity was considered present (P<0.1 and I^2>50%), we chose a random-effects model, otherwise, a fixed-effects model was used. The value of P less than 0.05 was regarded as statistically significant for all included studies.

RESULTS

Literature Search and Study Characteristics We identified 1545 potentially relevant studies from the initial search, and 1514 trials were excluded after a preliminary review. The remaining 31 studies were identified for detailed assessment. Finally, 4 RCTs and 10 retrospective chart series met the inclusion criteria. The selection process and reasons for exclusion are summarized in Figure 1[22-35].

The baseline characteristics of the participants and the design of the studies are summarized in Tables 1 and 2. Of the 4 RCT studies, two were conducted in the United States, and two in the United Kingdom and India each. The follow-up durations in all the included studies ranged from 2 to 24mo. Of the 15 studies, with age ranging from 63 to 90y, fourteen included both genders. For the study of Subramanian, there was only male patient in group B. Two RCTs had a Jadad

Table 1 Characteristics of included studies in the review of ranibizumab and bevacizumab for treatment of AMD

Study	Type of study	Data sources	No. of included patients		Male (%)		Age ($\bar{x} \pm s$, a)	
			Group R	Group B	Group R	Group B	Group R	Group B
Chang *et al*[23], 2009	Retrospectively	Retina Institute of California	107	69	43.5	33.3	78.3±8.8	79.6±9.8
Landa *et al*[25], 2009	Retrospectively	Retina Center of the New York Eye and Ear Infirmary	31	37	58.1	56.8	74.9±8.9	77.7±8.3
Gamulescu *et al*[26], 2010	Retrospectively	NS	30	30	30.0	36.7	77.2±7	77.5±6
Subramanian *et al*[22], 2010	RCT	Veterans Affairs Boston Healthcare System Hospital in Massachusetts	7	15	85.7	100.0	80	78
Fong *et al*[27], 2010	Retrospectively	Kaiser Permanente Southern California	128	324	39.1	43.5	81.8±7	78.2±9.3
Carneiro *et al*[30], 2010	Retrospectively	Department of Ophthalmology of the Hospital São João	219	97	NS	NS	77.74±7.40	77.82±7.75
Feng *et al*[28], 2011	Retrospectively	Lions Eye Institute	93	278	39.8	42.1	80.0±7.8	80.0±7.5
Biswas *et al*[29], 2011	RCT	Tertiary Hospital in Kolkata	54	50	40.7	56.0	63.48	63.36
Shah *et al*[24], 2009	Retrospectively	NS	49	25	36.7	36.0	77.0±9.08	80.0±7.30
Bellerive *et al*[31], 2012	Retrospectively	Centre Oculaire de Québec	50	147	29.0	36.0	76.9±8	76.4±8
Martin (monthly) *et al*[32], 2012	RCT	CATT	301	286	39.2	37.1	79.2±7.4	80.1±7.3
Martin (as needed) *et al*[32], 2012	RCT	CATT	298	300	37.9	38.7	78.4±7.8	79.3±7.6
Chakravarthy *et al*[33], 2012	RCT	IVAN	296	314	38.9	41.1	77.8±7.6	77.7±7.2
Sharma *et al*[34], 2012	Retrospectively cohort study	NS	351	173	36.8	42.2	78.7	76.9
De Bats *et al*[35], 2012	Retrospectively	Croix-Rousse University Hospital and Édouard-Herriot University Hospital	28	30	39.3	43.3	77	79

NS: Not specified; RCT: Randomized controlled trial; CATT: Comparison of AMD treatments trials; IVAN: Inhibit VEGF in age-related choroidal neovascularization randomized trial.

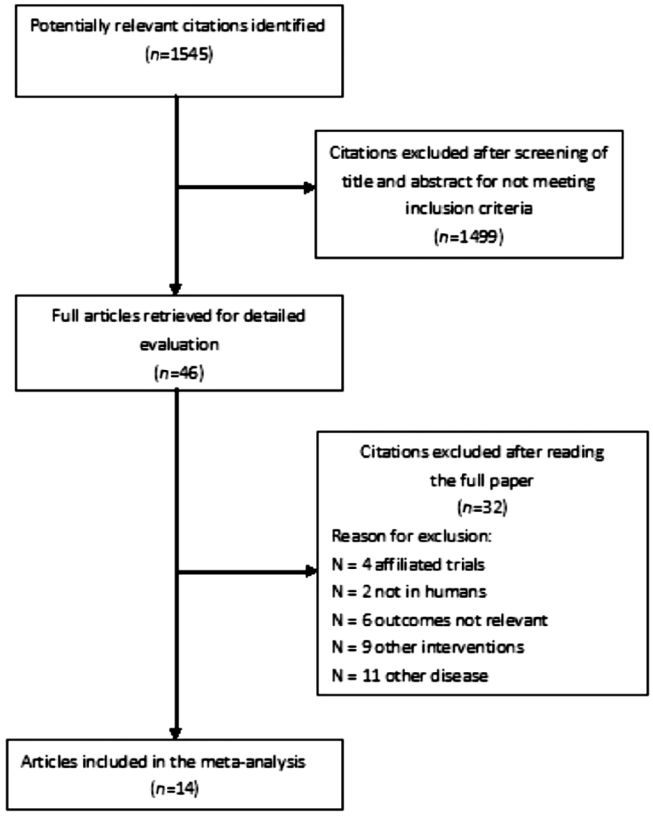

Figure 1 Flow chart of literature search and study selection.

score of 5, and the other two had a score of 3. For the non-RCTs, one trial had a NOS score of 8, two had a score of 7, each three had a score of 5 and 6, and the remaining one trial had a score of 3. In Tables 3-6 it shows the main results from each included study for our primary and secondary outcomes.

Visual Acuity and Best Corrected Visual Acuity Figure 2 shows the forest plots of 3 RCTs with 4 populations involving 1410 patients for the effect of VA. The mean difference of VA was not significant between the ranibizumab group and the bevacizumab group (WMD: -0.04; 95%CI: -0.08 to 0.00; P=0.06), with no evidence of heterogeneity (I^2=0%, P=0.61). Two studies reported data for the mean BCVA. The pooled result showed that the mean BCVA was not significantly different between the two groups (WMD: -0.05; 95%CI: -0.10 to 0.00; P=0.05, data not shown).

Retina Thickness and Foveal Thickness Figure 3 presents 3 studies involving 1448 patients for the effect of RT. The overall result showed that the mean RT was not significantly thinner in the ranibizumab group than the bevacizumab group (WMD: -4.69; 95%CI: -13.15 to 3.76; P=0.86). This finding was consistent for both RCTs (WMD: -4.83; 95%CI: -13.44 to 3.78; P=0.27) and non-RCTs (WMD: -0.86; 95% CI: -45.62 to 43.90; P=0.97). The heterogeneity test was not significant (I^2=0%, P=0.94).

Figure 4 shows the forest plot of 3 RCT studies and 3 non-RCT studies involving 1588 patients for the effect of FT. The overall result showed that the mean difference of FT was not significant between ranibizumab group and bevacizumab group (WMD: 10.91; 95%CI: -14.73 to 36.56; P=0.40), with a significant heterogeneity (I^2=84%, P< 0.0001). Subgroup analyses showed that the result was

Table 2 Details in treatment strategy of the included studies

Study	Duration of follow-up (mean or range)		Dosage (mg/0.05mL)		No. of injections per patient (mean)		Jadad score	NOS
	Group R	Group B	Group R	Group B	Group R	Group B		
Chang *et al*[23], 2009	3mo	3mo	0.5; 3 injection for every 4wk	1.25; 3 injection for every 6wk	NS	NS		6
Landa *et al*[25], 2009	9mo	8mo	0.5	1.25	5.5	5.0		7
Gamulescu *et al*[26], 2010	2-4mo		0.5; injection for every 4wk	1.25; injection for every 4wk	NS	NS		5
Subramanian *et al*[22], 2010	12mo		0.5l; every month for the first 3mo	1.25; every month for the first 3mo	4.0	8.0	5	
Fong *et al*[27], 2010	12mo		NS	NS	6.2	4.4		5
Carneiro *et al*[30], 2010	286.92±206.05d	832.63±268.73d	NS	NS	5.99±2.97	5.71±3.7		8
Feng *et al*[28], 2011	12mo		0.3	1.25	3.5±1.45	4.3±1.52		5
Biswas *et al*[29], 2011	18mo		0.5; 3 consecutive months	1.25; 3 consecutive months	5.6	4.3	3	
Shah *et al*[24], 2009	3mo		NS	NS	NS	NS		3
Bellerive *et al*[31], 2012	12mo		0.5; 3 monthly treatments	1.25; 3 monthly treatments	4.9	4.7		6
Martin (monthly) *et al*[32], 2012	24mo		0.5; every 28d	1.25; every 28d	NS	NS	5	
Martin (as needed) *et al*[32], 2012	24mo		0.5; signs of active neovascularization	1.25; signs of active neovascularization	NS	NS		
Chakravarthy *et al*[33], 2012	12mo		0.5	1.25	NS	NS	3	
Sharma *et al*[34], 2012	12mo		NS	NS	4.3	4.3		7
De Bats *et al*[35], 2012	12mo		0.5; every month	1.25; every month	5.8	4.8		6

NS: Not specified; RCT: Randomized controlled trial; d: Day; CATT: Comparison of AMD treatments trials; IVAN: Inhibit VEGF in age-related choroidal neovascularization randomized trial; NOS: Newcasle-Ottawa scale.

Table 3 Visual results from included studies in the review of ranibizumab and bevacizumab for treatment of AMD in RCTs

Study	VA	BCVA
Subramanian *et al*[22], 2010	Changes in ETDRS letters VA: group B improved from 34.9±14.5 to 42.5±13.7 *vs* group R improved from 32.7±20.9 to 39±10.1	NS
Biswas *et al*[29], 2011	NS	After the first 3 injections change in ETDRS letters BCVA: group B improved from 56.80 letters to 61.72 *vs* group R improved from 58.19 letters to 64. After 18mo change in ETDRS letters BCVA: group B improved from 56.80 letters to 60.76 *vs* group R improved from 58.19 letters to 61.74
Martin (monthly) *et al*[32], 2012	Change in ETDRS letters VA: group B improved from 60.2±13.6 letters to 68.2±16.1 *vs* group R improved from 59.9±14.2 letters to 68.5±18.9	NS
Martin (as needed) *et al*[32], 2012	Change in ETDRS letters VA: group B improved from 60.6±13.0 letters to 66.0±19.9 *vs* group R improved from 61.6±13.1 letters to 68.5±15.3	NS
Chakravarthy *et al*[33], 2012	Change in logMAR VA: group B decreased from 0.67±0.33 to 0.62±0.41 *vs* group R decreased from 0.66±0.34 to 0.57±0.38	Change in ETDRS letters BCVA: group B improved from 61.6±15.6 letters to 66.1±17.4 *vs* group R improved from 61.8±15.0 letters to 69.0±16.0

VA: Visual acuity; BCVA: Best corrected visual acuity.

consistent in both RCTs and non-RCTs.

Adverse Events Figure 5 shows the forest plot comparing the safety between ranibizumab and bevacizumab. In the pooled result of 3 RCTs and 1 non-RCT, more patients died in bevacizumab group compared to ranibizumab group. However, this difference was not statistically significant (RR: 0.92; 95%CI: 0.62 to 1.38; P=0.69; Figure 5A), with significant heterogeneity (I^2=0%, P=0.88). The overall result from 3 RCTs and 3 non-RCTs showed that ranibizumab was not associated with a reduction in the risk of arterial thromboembolic events (RR: 0.75; 95%CI: 0.16 to 3.42; P=0.71; Figure 5B), with consistent result in both RCTs and non-RCTs. The risk of ocular inflammation was reported in 2 RCTs and 7 non-RCTs. The overall result showed that ranibizumab was associated with a decreased risk of ocular inflammation compared to bevacizumab (RR: 0.45; 95% CI: 0.23 to 0.89; P=0.02; Figure 5C), without heterogeneity (I^2=45%, P=0.11). However, this finding was only significant in non-RCTs (RR: 0.40; 95% CI: 0.18 to 0.91; P=0.03). Figure 5D shows the forest plot of venous thrombotic events from 2 RCTs involving 1795 patients. The risk of venous thrombotic events was significantly less in the ranibizumab group than the bevacizumab group (RR: 0.27; 95%CI: 0.08 to 0.89; P=0.03). The heterogeneity test was not significant (I^2=0%, P=0.79). Five studies investigated the serious ocular adverse, with four of them having no

Table 4 Measurement of thickness results from included studies in the review of ranibizumab and bevacizumab for treatment of AMD in RCTs

Study	CMT	CFT	CRT
Subramanian *et al*[22], 2010	For the baseline: group B (-50 μm) *vs* R group (-90 μm)	NS	NS
Biswas *et al*[29], 2011	After 3mo change in CMT: group B decreased from 284 to 209.84 *vs* group R decreased from 288.63 to 217.07. After 6mo change in CMT: group B decreased from 284 to 225.28 *vs* group R decreased from 288.63 to 232.37. After 12mo change in CMT: group B decreased from 284 to 257.56 *vs* group R decreased from 288.63 to 261.04	NS	NS
Martin (monthly) *et al*[32], 2012	NS	Mean change from baseline group B (-180±196) group R (-190±172)	Mean change from baseline group B (-84±133) group R (-91±152)
Martin (as needed) *et al*[32], 2012	NS	Mean change from baseline group B (-153±189) group R (-166±190)	Mean change from baseline group B (-84±145) group R (-78±131)
Chakravarthy *et al*[33], 2012	NS	Change in CFT: group B decreased from 465±184 to 325±134 *vs* group R decreased from 468±187 to 322±139	Change in CRT: group B decreased from 264±131 to 180±92 *vs* group R decreased from 271±129 to 172±78

CMT: Central macular thickness; CFT: Central foveal thickness; CRT: Central retina thickness; NS: Not specified.

Table 5 Visual results from included studies in the review of ranibizumab and bevacizumab for treatment of AMD in non-RCTs

Study	VA	BCVA
Chang *et al*[23], 2009	After 3 treatments for the baseline: group B improved 4 letters *vs* group R improved 7 letters	NS
Landa *et al*[25], 2009	NS	Change in logMAR BCVA: group B decreased from 0.90±0.08 to 0.73 *vs* group R decreased from 0.91±0.07 to 0.77
Gamulescu *et al*[26], 2010	NS	After 1mo change in logMAR BCVA: group B decreased from 0.74 to 0.68 *vs* group R decreased from 0.76 to 0.70. After 2mo change in logMAR BCVA: group B decreased from 0.74 to 0.62 *vs* group R decreased from 0.76 to 0.63. After 5mo change in logMAR BCVA: group B decreased from 0.74 to 0.62 *vs* group R decreased from 0.76 to 0.58
Fong *et al*[27], 2010	Changes in Snellen VA(≥20/40): group B improved from 13.6% to 22.9% *vs* group R improved from 11.7% to 25%	NS
Carneiro *et al*[30], 2010	NS	NS
Feng *et al*[28], 2011	For the baseline: group B 24.5% gained 15 letters or more *vs* group R 25.8% gained 15 letters or more	NS
Shah *et al*[24], 2009	NS	NS
Bellerive *et al*[31], 2012	Change in logMAR VA: group B improved from 0.70 to 0.67 *vs* group R improved from 0.69 to 0.55	NS
Sharma *et al*[34], 2012	NS	NS
De Bats *et al*[35], 2012	NS	After 1mo change in logMAR BCVA: group B decreased from 0.70±0.46 to 0.63±0.51 *vs* group R decreased from 0.55±0.33 to 0.45±0.32. After 4mo change in logMAR BCVA: group B decreased from 0.70±0.46 to 0.48±0.37 *vs* group R decreased from 0.55±0.33 to 0.51±0.33. After 13mo change in logMAR BCVA: group B decreased from 0.70±0.46 to 0.47±0.37 *vs* group R decreased from 0.55±0.33 to 0.54±0.37

VA: Visual acuity; BCVA: Best corrected visual acuity.

events in both groups and one RCT [CATT 2012] indicating that the risk was lower in the ranibizumab group (RR: 0.79; 95%CI: 0.68 to 0.93; P=0.03, data not shown).

DISCUSSION

The studies included in this system review indicate robust efficacy and safety from ranibizumab and bevacizumab treatment based on RCTs and non-RCTs. The results of our meta-analysis suggest that ranibizumab and bevacizumab have equal clinical efficacy. However, the pooled analyses in the evaluation of safety showed that compared to bevacizumab, ranibizumab was associated with decreased risks of ocular inflammation and venous thrombotic events.

Although some systematic reviews investigated the efficacy and safety of ranibizumab and bevacizumab in AMD, the outcomes were assessed separately rather than a direct comparison and the conclusions were based on descriptive analysis [36]. In the present study, we included studies that compared the two drugs directly and found that the VA, RT

Table 6 Measurement of thickness results from included studies in the review of ranibizumab and bevacizumab for treatment of AMD in non-RCTs

Study	CMT	CFT	CRT
Chang *et al*[23], 2009	NS	For the baseline: group B decreased 20.2% *vs* group R decreased 29.2%	NS
Landa *et al*[25], 2009	NS	Change in CFT: group B decreased from 325±72 to 300±69 *vs* group R decreased from 307±57 to 289±56	NS
Gamulescu *et al*[26], 2010	NS	NS	Change in CRT: group B decreased from 317.87±105.77 to 264.17±77.72 *vs* group R decreased from 331.34±157.17 to 263.31±98.01
Fong *et al*[27], 2010	NS	NS	NS
Carneiro *et al*[30], 2010	NS	NS	NS
Feng *et al*[28], 2011	NS	NS	NS
Shah *et al*[24], 2009	NS	Change in CFT: group B decreased from 288±94 to 246±21 *vs* group R improved from 278±84 to 241±85	NS
Bellerive *et al*[31], 2012	NS	NS	NS
Sharma *et al*[34], 2012	NS	NS	NS
De Bats *et al*[35], 2012	After 1mo change in CMT: group B decreased from 369±77 to 307±76 *vs* group R decreased from 340±78 to 286±46. After 4mo change in CMT: group B decreased from 369±77 to 285±78 *vs* group R decreased from 340±78 to 299±82. After 13mo change in CMT: group B decreased from 369±77 to 284±87 *vs* group R decreased from 340±78 to 271±59	After 1mo change in CFT: group B decreased from 258±81 to 203±59 *vs* group R decreased from 264±87 to 215±60. After 4mo change in CFT: group B decreased from 258±81 to 198±53 *vs* group R decreased from 264±87 to 226±74. After 13mo change in CFT: group B decreased from 258±81 to 194±67 *vs* group R decreased from 264±87 to 203±62	NS

CMT: Central macular thickness; CFT: Central foveal thickness; CRT: Central retina thickness; NS: Not specified.

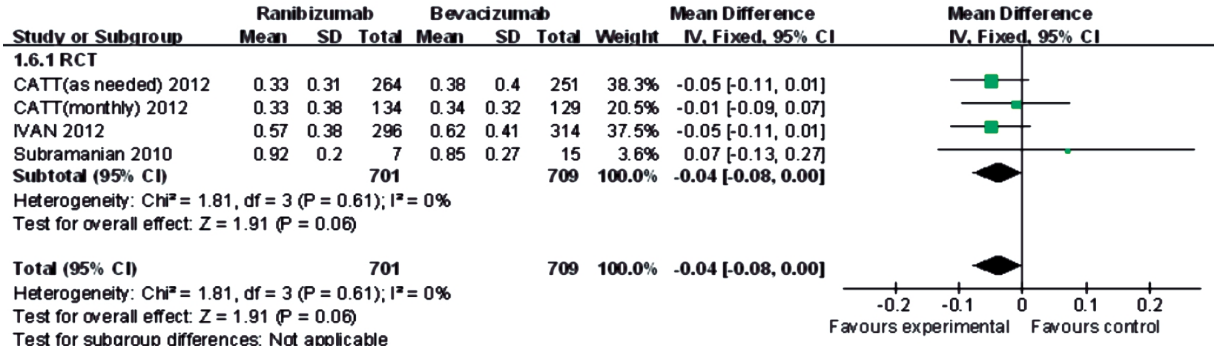

Figure 2 Forest plots for WMD of visual acuity after surgery comparing ranibizumab to bevacizumab.

and CFT of ranibizumab in the treatment of AMD were, at least, equivalent to those of bevacizumab.

The epitopes of ranibizumab and bevacizumab locate in the receptor-binding region of VEGF, and both antibodies target VEGF in a similar way[37]. However, bevacizumab (149 kDa) and ranibizumab (48.39 kDa) have different molecular weights, mainly because ranibizumab does not contain an Fc part. Moreover, bevacizumab is produced in a eukaryotic cell line and is N-glycosylated in its Fc region, but ranibizumab is expressed in prokaryotic E. coli without any glycosylation sites [38]. Therefore, the various molecular mechanisms of the drugs might result in different efficacy. Debates remained in the past years on whether ranibizumab or bevacizumab is superior in treating AMD. Chang *et al*[23] argued that being a smaller molecule, it is easier for ranibizumab to permeate the retina and inhibit abnormal blood vessel growth, thus leading to a better short-term efficacy of ranibizumab compared to bevacizumab. On the contrary, bevacizumab was found to be superior in long-term effects because of its decreased clearance from eye due to the larger size, and the consequent high accumulation in retinal pigment epithelial (RPE) cells[39]. In our study, no difference was observed between ranibizumab and bevacizumab in terms of efficacy, likely that many mechanisms interplay in the clinical practice and the management is perhaps more complicated than we assumed. More standard clinical trials are needed to be done

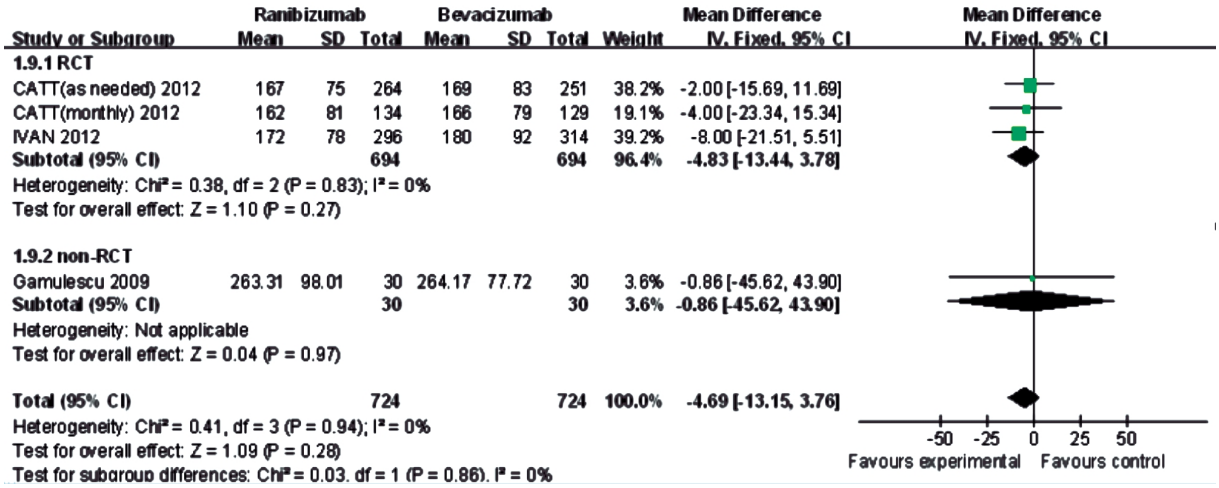

Figure 3 Forest plots for WMD of central foveal thickness after surgery comparing ranibizumab to bevacizumab.

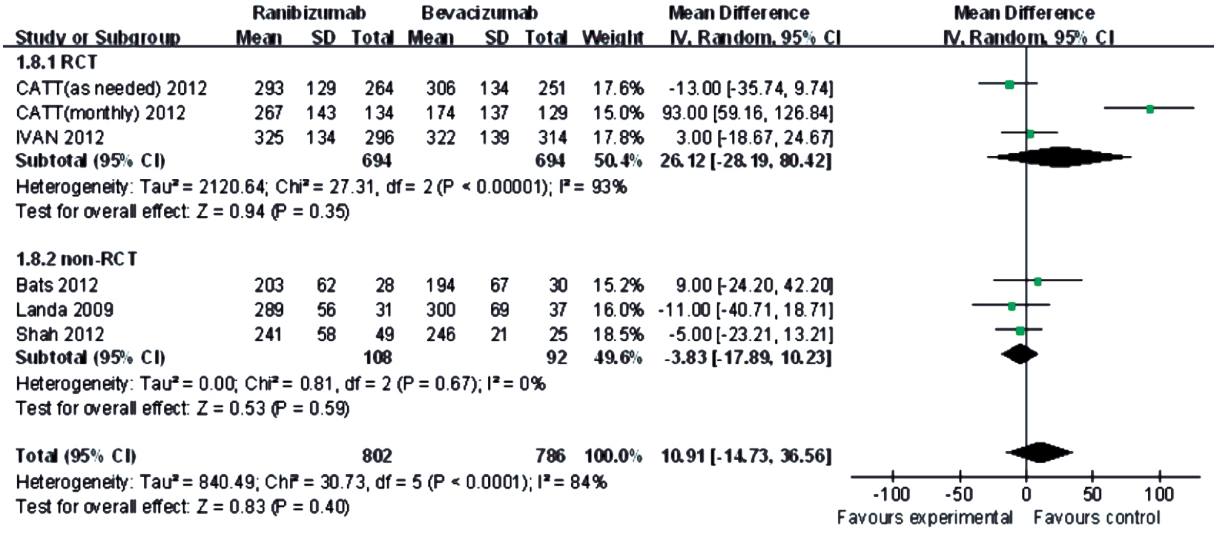

Figure 4 Forest plots for WMD of central retina thickness after surgery comparing ranibizumab to bevacizumab.

to conclude superiority.

Recently, intravitreal anti-VEGF drug injection has been reported with complications and adverse events, mainly including subconjunctival hemorrhage, cornea tear, ocular inflammation, uveitis, retinal detachment and cataract [40,41]. Some studies compare PDT with either intravenous ranibizumab or bevacizumab [42-45]. Intravitreal injection of ranibizumab was reported to be associated with endophthalmitis (≤2.1%), uveitis (≤1.3%), retinal detachment (≤1.5%), retinal tear (≤1.9%) and vitreous hemorrhage (≤8.0%) [42-44]. Compared to PDT group, an increase rate of pigment epithelial tears (5.5% *vs* 0.0%), posterior vitreous detachment (14.6% *vs* 0.0%) or cataract progression (7.3% *vs* 0.0%) was found in bevacizumab group in one RCT [45]. Although many studies assessed the safety of ranibizumab or bevacizumab comparing to control group, the comparison was not direct and likely led to an inconclusive result. In a previous meta-analysis, Schmucker *et al* [46] found that the difference of arterial thromboembolic events, serious nonocular hemorrhage and death were not statistically significant between the two drugs. But a pooled analysis of serious ocular adverse events indicated a significantly increased RR for bevacizumab when compared to ranibizumab [47]. In combination of 2-year follow-up result of CATT study and the new RCT IVAN trial, we found a higher risk of bevacizumab in ocular inflammation and venous thrombotic events, indicating a better safety profile of ranibizumab in AMD patients[32,33]. There were no substantial imbalances in demographic or ocular characteristics at baseline, indicating that the increased incidence of venous thrombosis is the result of truly higher risk. Regarding the safety profile of the two drugs, a previous meta-analysis including 11 studies, found that an increased risk of ocular and multiple systemic ocular adverse effects with bevacizumab, strengthening the better safety profile of R[47]. With equal efficacy and better safety profile compared to bevacizumab, ranibizumab seems to be the prior choice of AMD. However, the issue of expensiveness remains with ranibizumab.

Additionally, in some studies the effect of ranibizumab and bevacizumab on retinal conditions was compared. Singer *et al* [48] concluded that in patients with retinal vein

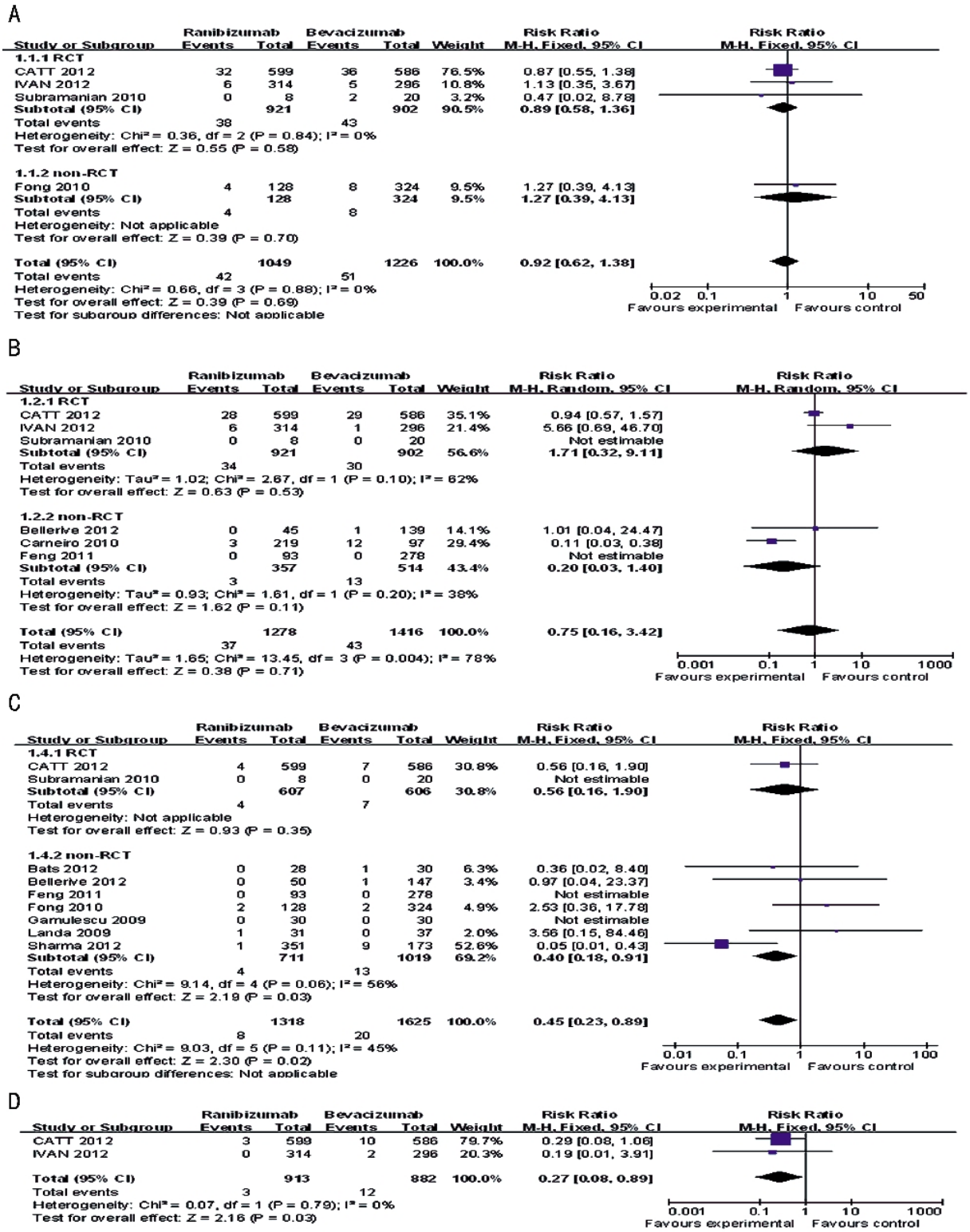

Figure 5 Forest plots: pooled results of head-to-head studies for different safety outcomes A: Death (any cause); B: Arterial ihromboembolic events; C: Ocular inflammation; D: Venous thrombotic events.

occlusions, ranibizumab appeared to have a greater short-term effect in decreasing macular edema on OCT when compared to bevacizumab. In another study by Niederhauser *et al* [49], the effect of bevacizumab or ranibizumab on visual acuity and central foveal thickness was evaluated in macular edema also resulted from retinal vein occlusion [48]. However no significant differences between bevacizumab and ranibizumab were found in the study[49].

The present study had several limitations. First, the publication bias cannot be fully ruled out. The number of studies included is insufficient to carry out a further statistical analysis to detect publication bias through asymmetry plot. Second, the studies included were heterogeneous in terms of study location, population and basal condition. We were not able to use individual-level data to improve the quality of adjustment and the precision

of estimates. Finally, the delay between literature search and publication was inevitable.

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