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Bevacizumab versus ranibizumab for neovascular age-related macular degeneration: a Meta-analysis

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Abstract

• AIM: To systematically compare the efficacy and safety of off-label bevacizumab versus licensed ranibizumab intravitreal injections as well as monthly regimen versus pro re nata [PRN (as needed)] regimen in the treatment of neovascular age-related macular degeneration (nAMD).

• METHODS: Relevant publications were identified through automatically retrieve of database and manually retrieving. The methodological quality of studies included was assessed using the Jadad score and the risk-of-bias assessment. The efficacy estimates were measured by the weight mean difference (WMD) for the improvement of best-corrected visual acuity (BCVA) and central retinal thickness (CRT) reduction. The safety estimates were measured by odds ratios (OR) for adverse events rates. Statistical analysis was conducted by Revman 5.2.7.

• RESULTS: Seven studies were included in the Meta-analysis. There were no statistically significant differences between bevacizumab and ranibizumab in BCVA at 1 and 2y (P=0.37, P=0.18, respectively), However, both drugs has better BCVA given monthly than given as needed at 1 and 2y (P<0.05). The results demonstrated the mean decrease in CRT was less in bevacizumab group than ranibizumab group at 1y (P<0.05), while the difference was not significant at 2y (P=0.24). Treatment monthly gained much more decrease in CRT at 1 and 2y (P<0.005).There were no differences between drugs in the rates of death, arterial thrombotic events and venous thrombotic events (P=0.41, P=0.55, P=0.10, respectively), while the rates of medical dictionary for regulatory activities (MedDAR) system organ class events and ≥1 systemic serious adverse events were higher in bevacizumab group than ranibizumab group (P<0.05). But the incidences of death, arterial thrombotic events, venous thrombotic events, MedDAR system organ class events as well as ≥1 systemic serious adverse events were not statistically different between both treatment regimens of monthly and as needed (P=0.14, P=0.76, P=0.73, P=0.12, P=0.11, respectively).

• CONCLUSION: Bevacizumab was equivalent to ranibizumab for BCVA, however bevacizumab tended to gain less decrease in CRT and had higher rates of serious adverse events. Compared with treatment as needed, treatment monthly showed superior efficacy in BCVA improvement and CRT reduction, while the rates of adverse events were similar in the two dosing regimens.

• **KEYWORDS:** bevacizumab; ranibizumab; neovascular age-related macular degeneration; Meta-analysis

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible severe vision loss among individuals aged 50y or older, and is classified into two types: dry (atrophic) AMD and wet (exudative) AMD[1,2]. Wet AMD is also known as neovascular AMD (nAMD), which is the most aggressive form [3]. Vascular endothelial growth factor-A (VEGF-A) has been implicated to play a major role in the pathogenesis of the nAMD [4-6]. The treatment for nAMD has been revolutionized with intravitreal anti-VEGF therapy: ranibizumab and bevacizumab[7,8].

Ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA), a humanized recombinant monoclonal anti-VEGF-A Fab fragment, is specifically designed for intravitreal treatment of nAMD. What is more, ranibizumab therapy is the first treatment for nAMD to improve vision for most patients, and has been approved by the US Food and Drug Administration for the treatment of nAMD on June 30, 2006[9,10]. Bevacizumab (Avastin; Genentech), a humanized full-length monoclonal antibody targeting VEGF-A and all of its isoforms, is primarily designed and approved for the intravenous treatment of metastatic colorectal cancer [11,12]. Although bevacizumab is still off-label for nAMD treatment, good efficacy and safety in masses of case series and

cost-effective make it commonly used in clinical treatment [13-15]. With the increase use of unlicensed bevacizumab and golden standard ranibizumab, comparative studies of them are in process in different countries, but the results are not consistent.

This Meta-analysis was performed to compare the efficacy and safety of bevacizumab versus ranibizumab for nAMD as well as monthly regimen versus as needed regimen. The results could be very important in choosing the better way of treatment for nAMD.

SUBJECTS AND METHODS

Search Strategy Medline, Embase, Web of Science and Cochrane Library were searched from inception until January 2014 with no limitations of language. The search strategy was based on combinations of medical subject headings and keywords. Search terms were "bevacizumab", "avastin", "ranibizumab", "lucentis", "AMD". A manual search was performed by checking the bibliographies of original reports and review articles to identify studies not yet included in the computerized databases.

Inclusion and Exclusion Criteria Inclusion in the Meta-analysis must met the following criteria: 1) study design: randomized controlled trials (RCTs); 2) population: nAMD patients aged more than 50 years old with any gender; 3) intervention: bevacizumab of 1.25 mg versus ranibizumab of 0.5 mg; 4) outcome variables: studies that have indicated at least one of best-corrected visual acuity (BCVA), central retinal thickness (CRT) and adverse events (AE) as the main outcome measures; 5) duration: follow-up time was not less than 1y. Exclusion criteria were as following: 1) meeting abstracts, full text without available raw data, duplicate publications, letters and reviews; 2) studies that were not RCTs; 3) studies of AMD but not nAMD.

Date Extraction Wang WJ and Zhang XL separately extracted the following data from all included researches: 1) characteristics of included studies: the name of first author or the study group, the year of publication, location of the trail, major inclusion criteria, patients age and sex ratio, number of subjects, various interventions, duration of follow-up; 2) means and standard deviations (SDs) of changes from baseline in BCVA in early treatment diabetic retinopathy study (ETDRS); 3) means and SDs of changes from baseline in CRT in μm; 4) rates of main AE including death, arterial thrombotic event, venous thrombotic event, medical dictionary for regulatory activities (MedDAR) system organ class and ≥1 serious systemic event [16]. Disagreement was resolved by discussion.

Qualitative Assessment The methodological quality of each study was assessed using the Jadad score and the risk-of-bias assessment [17,18]. In Jadad score assessment, a value of "2 points", "1 point" or "0 point" was assigned to the two aspects of random allocation and double blind, and a value of "1 point" or "0 point" was assigned to dropouts and withdrawals. The total score ranges from 0 to 5 points, and the studies with Jaded score ≥3 points were considered to have high quality. In the assessment of risk of bias, the following parameters were assessed: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome date; 6) selective reporting; 7) other biases. For the questions above, each parameter was judged of "yes" indicating low risk of bias, "no" indicating high risk of bias, and "unclear" indicating unclear or unknown risk of bias.

Statistical Analysis The quantitative data were entered into Cochrane Review Manager (RevMan, software version 5.2, Copenhagen: The Nordic Cochrane Center, The Cochration, 2012). For continuous variables (BCVA and CRT), weighted mean differences (WMD) were calculated, while the odds ratios (OR) were measured for dichotomous variables (AE). All of the outcomes were provided with a 95% confidence interval (CI). $P<0.05$ was considered as statistically significant on the test for overall effect. The Chi-square test and I^2 statistic were calculated to assess heterogeneity between trails. The fixed effects model was used for pooling the data when there was no statistical heterogeneity ($P>0.1$, $I^2<50\%$). Alternatively, if there was heterogeneity between studies ($P\leq0.1$, $I^2\geq50\%$), the random-effects model was applied to combining the data.

RESULTS

Literature Search The flow diagram of search results was shown in Figure 1. A total of 89 potentially relevant articles were identified through multiple database searches before January in 2014. Eight RCTs were retrieved on comprehensive full-text review, of which one study was excluded because of inappropriate outcome [19]. Only seven RCTs were included for this Meta-analysis.

Characteristics of Eligible Studies The main characteristics of the seven RCTs included in the Meta-analysis are shown in Table 1. The trials included were undertaken in various countries, including USA, Austria, France and UK. The mean age ranged from 76.7 to 80.4y. The number of male was a little less than female on the whole. Among the comparison groups, baseline characteristics were balanced, and the duration of follow-up was 1 or 2y. The studies were published between 2010 and 2013.

Quality Assessment All the RCTs included were evaluated for methodological quality according to the Jadad score. All RCTs proved to be of high qualification. A risk of bias summary for publication was shown in Figure 2. In the seven RCTs included in this Meta-analysis, concerning selection bias, the sequence generation and allocation concealment was appropriate in six studies, only the study of Subramanian *et al*[20] was unclear. Participants and personnel of all studies

Table 1 Characteristics of the included seven randomized controlled trails

Study	Country	Major inclusion criteria	Mean age	M/F	No. of eyes	Intervention groups	Follow-up (a)	Jadad Score
Subramanian 2010	USA	Symptomatic CNV secondary to AMD and affecting foveal centre by FFA and OCT; BCVA: 20/40-20/200	78.0	15/0	15	B	1	4
			80.0	6/1	7	R		
MANTA 2013	Austria	Active primary or recurrent CNV secondary to AMD, BCVA: 20/40-20/320	76.7±7.8	56/98	154	B	1	4
			77.6±8.1	59/104	163	R		
GEFAL 2013	France	Active nAMD and totol CNV area<12 optic DA; BCVA: 20/32-20/320	79.6±6.9	72/119	191	B	1	3
			78.7±7.2	54/129	183	R		
CATT 2011	USA	Previously untreated active CNV due to AMD; BCVA: 20/25-20/320	80.1±7.3	106/180	286	B monthly	1	4
			79.2±7.4	118/183	301	R monthly		
			79.3±7.6	116/184	300	B as needed		
			78.4±7.8	113/185	298	R as needed		
IVAN 2012	UK	Previous untreated nAMD and BCVA≥25 letters	77.7±7.2	115/181	296	B	1	5
			77.8±7.6	129/185	314	R		
			77.8±8.0	126/182	308	monthly		
			77.6±6.8	118/184	302	as needed		
CATT 2012	USA	Active CNV secondary to AMD and no previous treatment; BCVA: 20/25-20/320	79.7±7.5	53/82	135	B monthly	2	4
			79.5±7.4	56/90	146	R monthly		
			78.9±7.4	104/166	270	B as needed		
			78.3±7.8	108/179	287	R as needed		
			80.4±7.1	45/86	131	B switched		
			78.8±7.5	56/82	138	R switched		
IVAN 2013	UK	Active and previously untreated nAMD; BCVA≥25 letters.	77.7±7.2	115/181	296	B	2	5
			77.8±7.6	129/185	314	R		
			77.8±8.0	126/182	308	monthly		
			77.6±6.8	118/184	302	as needed		

AMD: Age-related macular degeneration; nAMD: Neovascular AMD; CNV: Choroidal neovascularization; B: Bevacizumab; R: Ranibizumab; BCVA: Best-corrected visual acuity; DR: Diabetic retinopathy; OCT: Optic coherence tomography; FFA: Fundus fluorescence angiography.

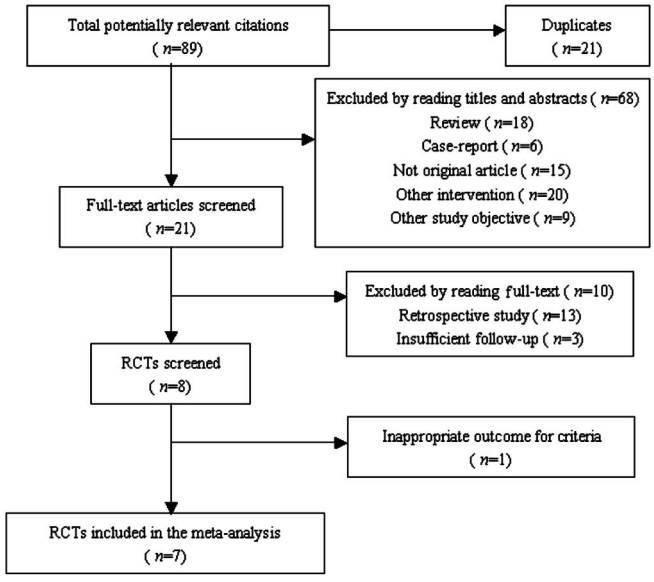

Figure 1 Flow diagram of literatures screening.

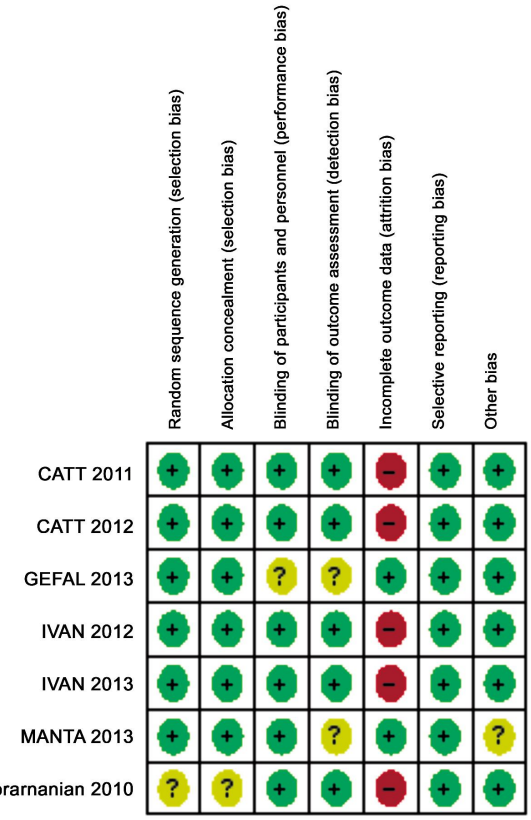

Figure 2 Risk of bias summary for each included study (+: low risk of bias; -: high risk of bias; ?: unclear risk of bias).

were blinded except that the trail of GEFAL Study Group[21] was unclear. The blinding of outcomes assessment was reported in five studies and the other two were unclear. There were missing data in outcomes in the studies of CATT Research Group [22,23] and IVAN Study Investigators [24,25] as well as Subramanian *et al* [20]. Selective outcomes reporting

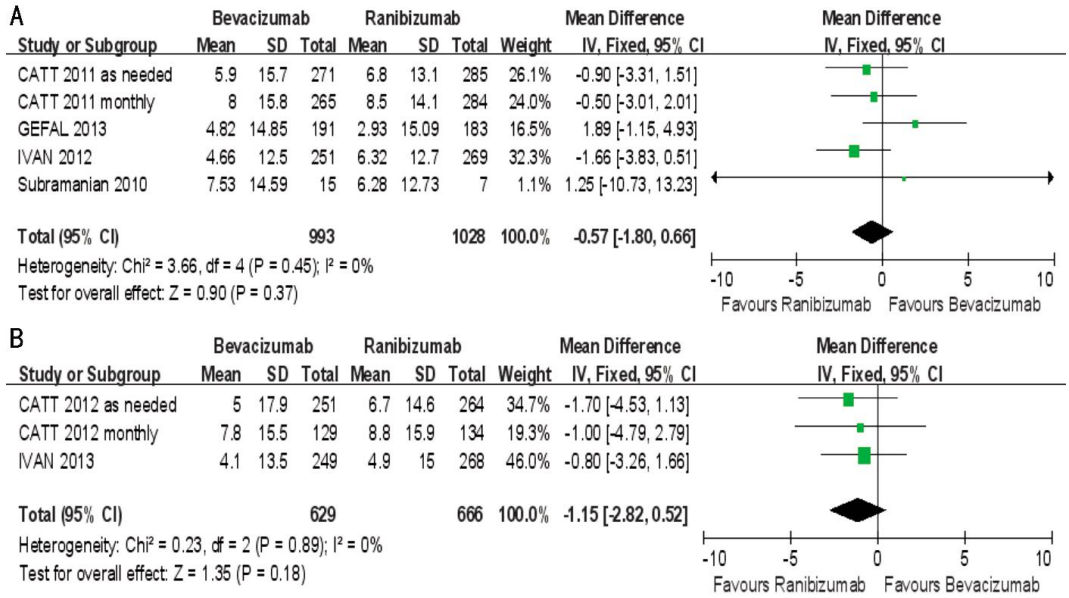

Figure 3 Forest plots for mean difference in BCVA in diabetic retinopathy study (ETDRS) along with the associated 95% CI in bevacizumab group versus ranibizumab group A: at 1y; B: at 2y.

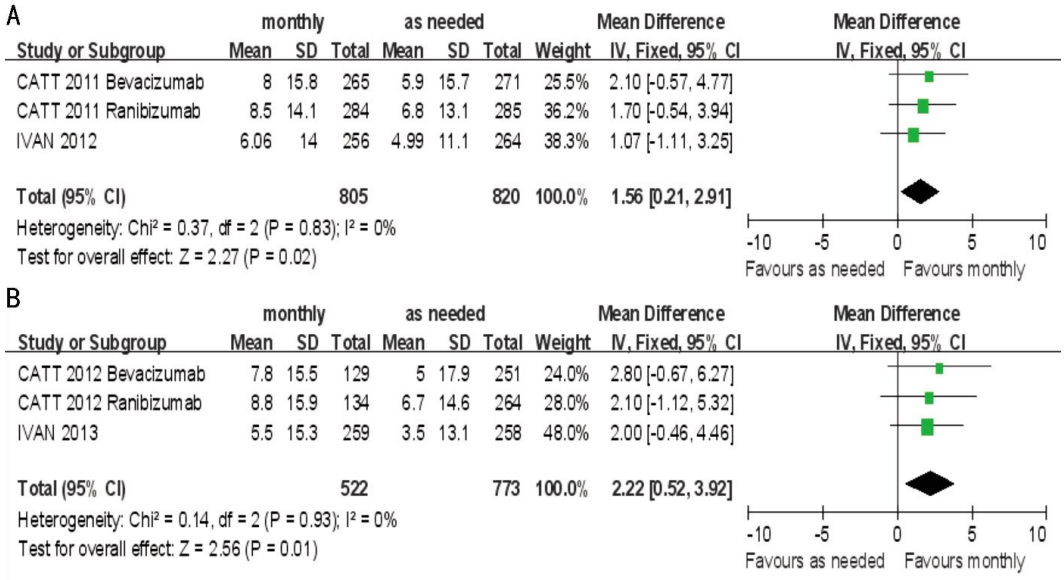

Figure 4 Forest plots for mean difference in BCVA in ETDRS along with the associated 95% CI in monthly regimen group versus as needed regimen group A: at 1y; B: at 2y.

were avoided in all RCTs. Two studies used single-blind and five studies used double-blind.

Efficacy Analysis Best-corrected Visual Acuity The pooled WMDs of the changes in BCVA (on ETDRS chart) comparison between bevacizumab and ranibizuman are shown in Figure 3. Representing the functional outcome, BCVA was detected to improve in both drugs. Although ranibizumab tended to have more BCVA improvement, the difference was not significant at 1y follow-up (WMD, -0.57; 95%CI, -1.80 to 0.66, P=0.37) and at 2y follow-up (WMD, -1.15; 95%CI, -2.82 to 0.52, P=0.18), with no heterogeneity identified at 1y (I^2=0%, P=0.45) and 2y (I^2=0%, P=0.89). However, the changes of BCVA between the two regimens of monthly and as needed were statistically different in favor of monthly dosing regimen both at 1y (WMD, 1.56; 95% CI, 0.21 to 2.91, P=0.02) and at 2y (WMD, 2.22; 95% CI, 0.52 to 3.92, P=0.01), and no statistical heterogeneity was observed at 1y (I^2=0%, P=0.83) and at 2y (I^2=0%, P=0.93; Figure 4).

Efficacy Analysis-central Retinal Thickness On behalf of the anatomic outcome, CRT was revealed to reduce in both drugs and two administration regimens of drugs. Ranibizumab was detected to have greater reduction in CRT comparing with bevacizumab. A statistical difference was found at 1y (WMD, 16.12; 95%CI, 2.01 to 30.23, P=0.03), while the difference was not significant at 2y (WMD, 11.79; 95%CI, -7.74 to 31.32, P=0.24). No significant heterogeneity was found at the follow-up of 1y (I^2=0%, P=0.66) and 2y (I^2=0%, P=0.99; Figure 5). The results suggested that monthly regimen gained more reduction of CRT than as

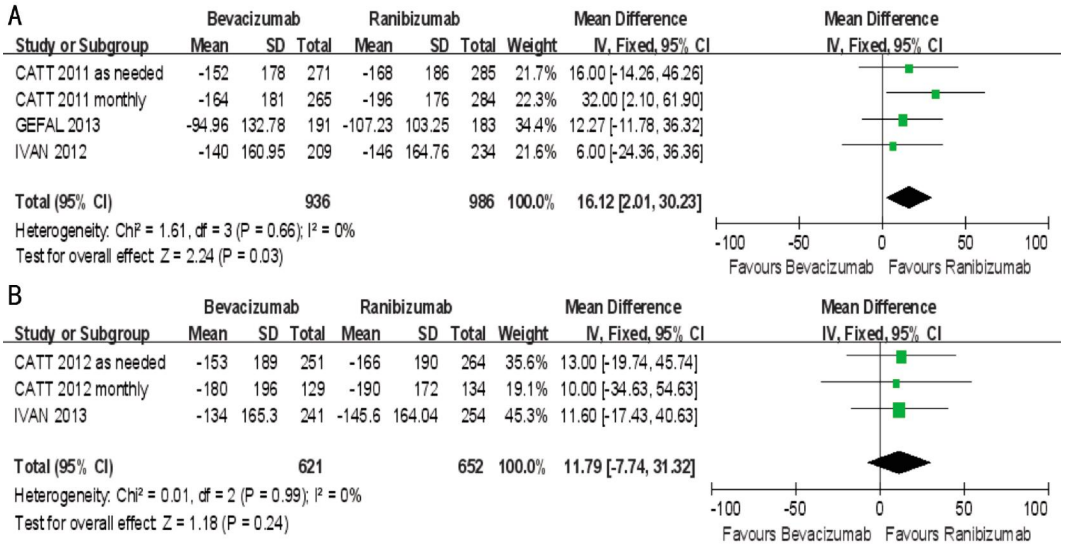

Figure 5 Forest plots for mean difference in CRT (μm) along with the associated 95% CI in bevacizumab group versus ranibizumab group A: at 1y; B: at 2y.

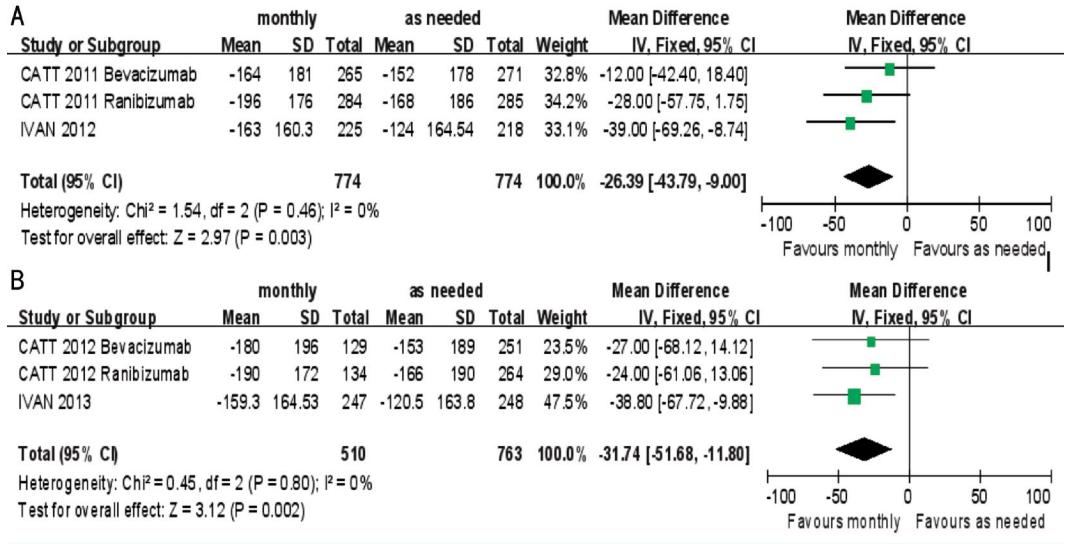

Figure 6 Forest plots for mean difference in CRT (μm) along with the associated 95% CI in monthly regimen group versus as needed regimen group A: at 1y; B: at 2y.

needed regimen with statistical significance, indicating that dosing regimen of monthly tend to have a better anatomic outcome. The WMD was -26.39 (95%CI, -43.79 to -9, P=0.003) with no heterogeneity (I^2=0%, P=0.46) at 1y, and the WMD was -31.74 (95%CI, -51.68 to -11.80, P=0.002) with no heterogeneity (I^2=0%, P=0.80) at 2y (Figure 6).

Safety Analysis Serious AE after treatment comparing bevacizumab to ranibizumab are shown in Figure 7. There were no significant differences between bevacizumab and ranibizumab with respect to the incidences of death (OR=1.28; 95% CI, 0.71 to 2.33, P=0.41), arterial thrombotic event (OR=0.82; 95% CI, 0.42 to 1.59, P=0.55), venous thrombotic event (OR=2.78; 95%CI, 0.82 to 9.44, P=0.10), with no heterogeneity (I^2=0%, P=0.71; I^2=0%, P=0.41; I^2=0%, P=0.42, respectively). The bevacizumab was associated with a statistically higher frequency of MedDAR system organ class event (OR=1.52; 95%CI, 1.21 to 1.92, P=0.0004) and ≥1 serious systemic event (OR=1.35; 95% CI, 1.05 to 1.72, P=0.02), with no heterogeneity identified (I^2=21%, P=0.28; I^2=0%, P=1.0, respectively).No significant differences were found between dosing regimens of monthly and as needed in the incidence of any analyzed AE, including death (OR=0.59; 95%CI, 0.30 to 1.18, P=0.14), arterial thrombotic event (OR=0.90; 95%CI, 0.45 to 1.77, P=0.76), venous thrombotic event (OR=1.24; 95%CI, 0.36 to 4.31, P=0.73), MedDAR system organ class event (OR=0.81; 95% CI, 0.63 to 1.05, P=0.12) as well as ≥1 serious systemic event (OR=0.82; 95%CI, 0.64 to 1.05, P=0.11), all with no heterogeneity identified (P=0.59, P=0.84, P=0.27, P=0.52, P=0.97, respectively; Figure 8).

Sensitivity Analysis The study by MANTA Research Group [26] comparing the mean reduction of CRT from baseline after bevacizumab and ranibizumab treatment, outcomes of which were far different from the others, was

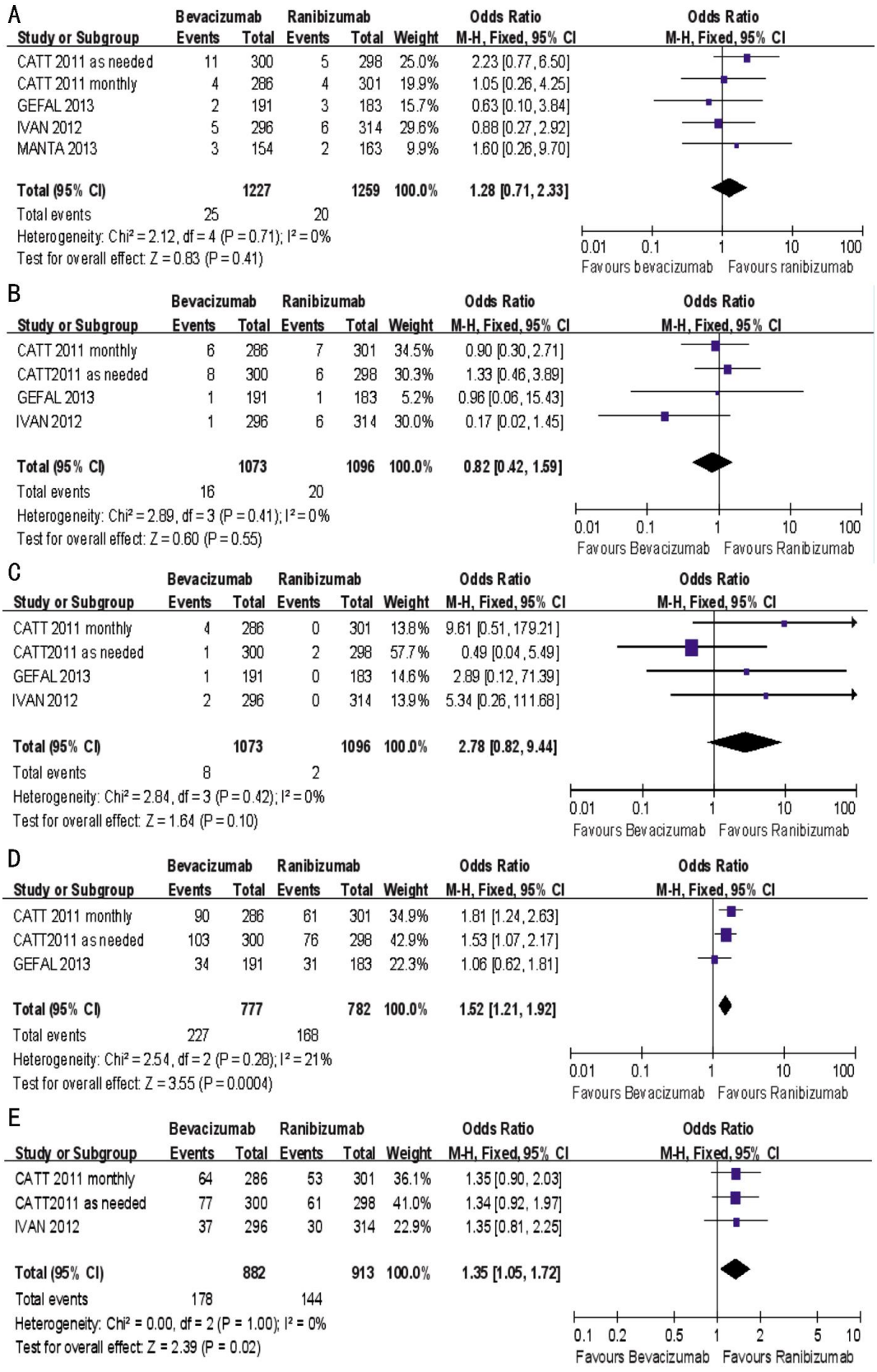

Figure 7 Forest plots for the proportion of patients in AE in bevacizumab group versus ranibizumab group at 1y A: Death; B: Arterial thrombotic events; C: Venous thrombotic event; D: MedDAR system organ class; E: ⩾1 serious systemic event.

excluded. Removing the study did not alter the result obtained in previous analysis.

DISCUSSION

Lots of studies concluded bevacizumab and ranibizumab had similar visual and anatomic outcome for nAMD, and that bevacizumab was much less expensive than the gold standard ranibizumab, all of these giving rise to the widespread use of bevacizumab[27-30]. However, the studies by Chang *et al* [31] and GEFAL Study Group [21] demonstrated that the effectiveness of ranibizumab treatment measured by

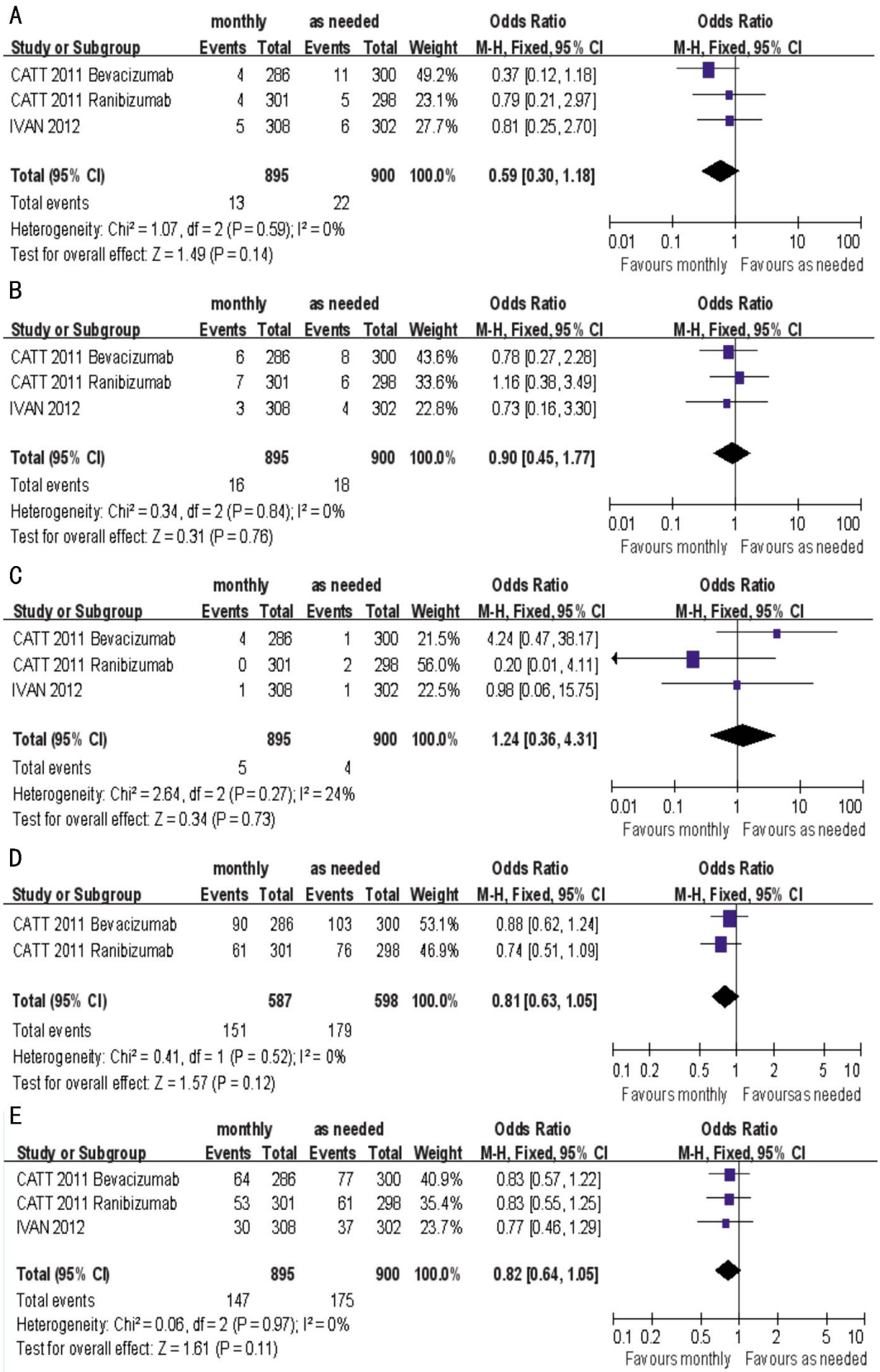

Figure 8 Forest plots for the proportion of patients in AE in monthly regimen group versus as needed regimen group at 1y
A: Death; B: Arterial thrombotic events; C: Venous thrombotic event; D: MedDAR system organ class; E: ⩾1 serious systemic event.

incremental improvement in optical coherence tomography parameters was significantly greater than bevacizumab treatment, meaning that off-label bevacizumab was inferior to licensed ranibizumab for anatomic result. And other study concluded that there were persist higher rates of serious AE with bevacizumab treatment than ranibizumab treatment [23]. Hence it is still unknown that whether the two biologic are equivalent or which certain is more effective. Thus, we conducted this Meta-analysis to compare the efficacy and safety of intravitreal bevacizumab and ranibizumab in the

treatment of nAMD.

In our analysis, we found that intravitreal bevacizumab was as effective as ranibizumab in the mean improvement of BCVA from baseline, however, bevacizumab was associated with less reduction in CRT than ranibizumab. There was more likely to be no absolute correlation between the visual function outcome and the change in anatomic outcome. This finding was in good agreement with the conclusions of Moutray *et al* [32] and Unver *et al* [33], who studied the relationship between visual function and anatomic changes in the treatment of nAMD. By comparing the different dosing regimens of monthly and as needed, we discovered that the monthly regimen was more effective in improving BCVA and reducing the CRT than as needed regimen. The dosing regimens were also discussed by many studies. Haller [34] pointed out that as needed regimen provided a reasonable approach to monthly but individualization of treatment needed to continue to evolve. Gupta *et al* [35] concluded monthly administration achieved greater visual gains than as needed protocol, consistent with our results.

Our analysis showed that the incidences of serious systemic event and MedDAR System Organ Class event in the treatment of bevacizumab were statistically higher than ranibizumab, while the rates of death and thrombotic event had no difference. Moreover, the rates of all AE in different dosing regimens made no odds. The reason may be related to the not exactly same characteristics of the two drugs, but still uncertain. Although bevacizumab like ranibizumab is a monoclonal antibody inhibiting all isoforms of VEGF, bevacizumab is a larger molecule of 149 KD and has longer half-life of 17-21d than ranibizumab weight of 48.38 KD and half-life of 3d[36]. Carneiro *et al* [37] concluded that intravitreal bevacizumab significantly reduced VEGF plasma levels until 28d after intravitreal injection in patients with nAMD while ranibizumab did not achieve a significant plasma VEGF reduction at the same time-point. These alert to the potential systemic safety differences between the two drugs after intravitreal administration. In addition, VEGF is important for reperfusion in the body, and patients with lower systemic level of VEGF-A are likely to have lower thresholds of tolerance to anti-VEDF agents and are at higher risk for systemic AE[38].

In our inclusion, the proportion of patients with pigment detachment (PED) associated with nAMD was similar in bevacizumab group and ranibizumab group at baseline in the study by GEFAL Study Group [21], and there was no specific description of the proportion of patients with PED at baseline in other studies. PED, which refers to separation of the retinal pigment epithelium (RPE) from the underlying Bruch membrane, is common in patients with AMD. In nAMD, occult choroidal neovascularization (CNV) are frequently accompanied by a PED, and the prevalence of a PED has been reported to be 10%-22% in eyes with typical nAMD[39,40]. Numerous studies showed that intravitreal bevacizumab and ranibizumab were effective and safe for improving vision in nAMD patients with PED especially serous PED, and the anatomic response of the PED may not correlate directly with the visual outcome [41-43]. However, Lommatzsch *et al*[40] pointed out that although treatment with bevacizumab and ranibizumab produced better morphological and visual results, only a partial flattening of the PED and cannot avoiding RPE tears indicating a worse prognosis. Introini *et al* [44] concluded that there is no effective therapy for PED secondary to nAMD, suggesting that anti-VEGF therapy could achieve only stabilization of the disease, but with high risk of RPE tear. Moreover, Bolz *et al*[45] reported that a high PED at baseline was found to be a negative predictive factor for visual outcome in nAMD. Long-term treatment strategies and prognosis should be defined.

The present Meta-analysis is a purely completely classical pairwise Meta-analysis, comparing the efficacy and safety of bevacizumab versus ranibizumab as well as monthly regimen versus as needed regimen in the treatment of nAMD. This Meta-analysis is different from the previous Meta-analysis by Schmucker *et al* [46], which was not absolutely a direct comparison of the two drugs and had less head to head trails. Our findings indicated that bevacizumab and ranibizumab were equivalent in improving BCVA, while ranibizumab seemed to have more reduction in CRT and tended to be safer. Advese events rates had no difference in the two dosing regimens, but monthly regimen proved to be more effective than as needed regimen. However, some limitations may be found in our analysis. First, some useful studies could not be included due to inadequate follow-up time, resulting in a relatively small sample size of our study. Second, although we conducted a thorough electronic serch and a manual search of the references of relevant results to minimize publication bias, there were not sufficient studies included to verify if asymmetry exists in a funnel plot. Consequently, a mass of RCTs with longer duration and larger sample size are needed to confirm our results further.

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Conflicts of Interest: Wang WJ, None; **Chen J,** None; **Zhang XL,** None; **Yao M,** None; **Liu XY,** None; **Zhou Q,** None; **Qu YX,** None.

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