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Combination of ranibizumab with photodynamic therapy *vs* ranibizumab monotherapy in the treatment of age-related macular degeneration: a systematic review and meta-analysis of randomized controlled trials

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Abstract

• AIM: To compare the efficacy and safety of combination of ranibizumab with photodynamic therapy (PDT) *vs* ranibizumab monotherapy in the treatment of age-related macular degeneration (AMD).

• METHODS: The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Pubmed, and Embase were searched. There were no language or data restrictions in the search for trials. Only randomized controlled trials (RCTs) were included. Methodological quality of the literatures was evaluated according to the Jadad Score. RevMan 5.2.6 software was used to do the meta-analysis.

• RESULTS: Seven studies were included in our systematic review, among which four of them were included in quantitative analysis. The result shows that the ranibizumab monotherapy group had a better mean best corrected visual acuity (BCVA) change *vs* baseline at month 12 compared with that of the combination treatment group, and the statistical difference was significant (WMD, -2.61; 95% CI, -5.08 to -0.13; *P*=0.04). However, after the removal of one study, the difference between the two groups showed no significant difference (WMD, -2.29; 95% CI, -4.81 to 0.23; *P*=0.07). Meanwhile, no significant central retinal thickness (CRT) reduction was found in the combination treatment group and the ranibizumab monotherapy group at 12 months follow-up. Nevertheless, the combination group tended to have a greater reduction in CRT (WMD, -4.13μm; 95%CI, -25.88 to 17.63, *P*=0.71). The proportion of patients gaining more than 3 lines at month 12 in the ranibizumab group was higher than in the combination group and there was a significant difference (RR, 0.72; 95% CI, 0.54 to 0.95; *P*= 0.02). Whereas there was no significant difference for the proportion of patients gaining more than 0 line at month 12 between the two groups (RR, 0.93; 95% CI, 0.76 to 1.15; *P*=0.52). The general tendency shows a reduction in ranibizumab retreatment number in the combination treatment group compared with the ranibizumab monotherapy group. As major adverse events, the differences in the number of eye pain, endophthalmitis, hypertension and arterial thromboembolic events were not significant between the two groups, and the incidence of serious adverse events in the two groups was very low.

• CONCLUSION: For the maintenance of vision, the comparison of the combination of ranibizumab with PDT *vs* ranibizumab monotherapy shows no apparent difference. Compared with the combination of ranibizumab and PDT, patients treated with ranibizumab monothearpy may gain more visual acuity (VA) improvement. The combination treatment group had a tendency to reduce the number of ranibizumab retreatment. Both the two treatment strategies were well tolerated.

• KEYWORDS: ranibizumab; photodynamic therapy; age-related macular degeneration; meta-analysis
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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe visual impairment in people older than 50y of age [1]. The neovascular type is characterized by the presence of choroidal neovascularisation (CNV) [2]. The pathophysiology of neovascular AMD is complex, involving both angiogenic and inflammatory components [3]. Symptoms of neovascular AMD usually begin with central visual blurring, distortion or a scotoma. When the eyes are both affected by AMD, patients ultimately lose the ability to read, drive or see fine details such as facial expressions and features [4]. So, the loss of central vision caused by neovascular AMD has a tremendous impact on the quality of patients' life.

Currently, the most commonly used treatment options for AMD are verteporfin photodynamic therapy (PDT) and intravitreal injections with inhibitors of vascular endothelial growth factor (VEGF)-A[4]. Verteporfin binds to low-density lipoprotein receptors in the plasma during the infusion, which is then preferentially bound by choroidal neovascular tissue which expresses low-density lipoprotein receptors. Irradiation of the neovascular lesion by the laser creates toxic reactive oxygen species that induce thrombosis and closure of the CNV [5].The efficacy and safety of PDT in neovascular AMD were demonstrated in the phase III Verteporfin In Photodynamic Therapy (VIP) trial and Treatment of AMD with Photodynamic Therapy (TAP) investigations [6-8] . In the past, PDT was considered the standard therapy for patients with classic subfoveal CNV due to neovascular AMD [9]. However, visual outcomes, as described in the literature [10], were not satisfactory. Furthermore, other adverse effects of PDT include choroidal hypoperfusion, pigment epithelium atrophy, inflammation, upregulation of VEGF production and scarring induced by irradiation [11]. Ranibizumab, the antigen-binding fragment of a recombinant humanized monoclonal antibody that binds with high affinity and can inhibits the biological activity of multiple isoforms of VEGF, has been approved by the United States Food and Drug Administration for the treatment of neovascular AMD in 2006 [12]. Many clinical trials have indicated that ranibizumab (used a fixed, monthly dosing regimen) is better than PDT as monotherapy in improving visual acuity [13-15]. However, monthly dosing regimens will increase the requirement of follow-up visits and expose patients to the risk of side effects like endophthalmitis [16,17]. Since these two regimens target different components of CNV, combination treatment of verteporfin PDT and intravitreal injection of ranibizumab may have a beneficial synergistic effect that could reduce the number of retreatment and increase durability of response compared with ranibizumab monotherapy, while maintaining VA outcomes. Besides, direct VEGF inhibition in combined treatment can not only reduce the interior inflammation of neovascularization, but also limit the edema caused by nonthermal laser and suppress angiogenic mediators upregulated by PDT [17]. The PrONTO study suggested that a pro re nata (PRN) approach to retreatment could meet the goal of visual maintenance while easing the treatment burden[18]. Nevertheless, the ideal maintenance regimen is still an area of scientific debate. A randomized clinical controlled trial has revealed that a combination of PDT and ranibizumab could reduce the number of required ranibizumab injections [19]. Whereas another study showed no benefit in reducing the number of ranibizumab retreatment [20]. Therefore, we undertook a systematic review of randomized controlled trials to evaluate the efficacy and safety of verteporfin PDT and intravitreal ranibizumab combination treatment *vs* ranibizumab monotherapy in patients with AMD.

SUBJETCS AND METHODS

Search Strategy To find the relevant literatures, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Pubmed, and Embase were searched. Meanwhile, reference lists of included trials were also searched. There were no language or data restrictions in searching trials. The date of searching databases ended September 1, 2013. The search strategy was based on combinations of medical subject headings and free text word and the search terms used were "ranibizumab", "lucentis," "photodynamic therapy," "age-related macular degeneration," and "randomized controlled trials" in various combinations. Retrieved articles were imported into EndNote X6 where duplicate articles were manually removed.

Inclusion and Exclusion Criteria Published studies, regardless of sample size, were included if they 1) included human eyes with active CNV secondary to AMD; 2) were randomized controlled trials (RCTs) which compared combination of ranibizumab with PDT *vs* ranibizumab monotherapy; and 3) reported one or more of the following outcomes: best-corrected visual acuity (BCVA), central retinal thickness (CRT), number of treatments, and ocular or systemic adverse events. Exclusion criteria were: 1) studies which were not randomized controlled trials; 2) studies of CNV secondary to causes other than age-related macular degeneration. We also excluded conference abstracts that had not been published. If two or more reports were based on the same group of patients, these reports would be combined as a single study. Article titles were screened for eligibility by two reviewers independently, and abstracts or full texts were reviewed as necessary.

Data Extraction and Quality Assessment Two review authors (Jun-Kang Si, Kai Tang) independently extracted the data from articles that met this study's inclusion criteria. Two authors resolved inconsistencies by discussion and consensus. The following data were extracted from articles that met this study's inclusion criteria: 1) Basic data: name of first author,

the year of publication and location of the study, major inclusion criteria and major exclusion criteria, various intervention groups, number of subjects, patient age, gender, duration of follow-up; 2) outcomes: means and standard deviations (SD) of BCVA and CRT change *vs* baseline at month 12, the number of patients with visual gaining in BCVA of more than 0 or 3 lines on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at month 12, the number of cases which had eye pain, hypertension, endophthalmitis and arterial thromboembolic events, and the number of ranibizumab retreatment after a loading dose of three intravitreal ranibizumab injections.

The methodological quality of the articles was evaluated using the Jadad scale [21]. This validated approach assesses randomization (0-2 points), blinding (0-2 points), and withdrawals (0-1 point) on a 5-point scale. The studies were considered to be of low quality if the Jadad score is ≤2 and high quality if the score is ≥3 [22]. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Statistical Analysis Statistical analysis was performed with RevMan 5.2.6 software supplied by Cochrane Collaboration. In our meta-analysis, the effect sizes of each study were presented as mean difference with 95% confidence intervals (CI) for continuous data, and as risk ratio with 95% CI for dichotomous data. Weighted mean difference and pooled risk ratio were then calculated by fixed-effect model or random-effect model depending on the significance of heterogeneity. We evaluated clinical heterogeneity according to the baseline characteristics and treatment. We estimated statistical heterogeneity by I-square (I^2) statistic. The statistical heterogeneity was considered significant when I^2 statistic was ≥50%. We also performed sensitivity analysis by omitting one study and reconducting meta-analysis with remaining studies. The pooled effect sizes were considered significant when the 95% CI of weighted mean difference did not cross zero or when the 95% CI of pooled risk ratio did not cross 1.0.

RESULTS

Study Description Figure 1 shows in a flow chart format the process of filtering articles to determine their appropriate value for inclusion in the meta-analysis and review. A total of 181 studies were initially identified, of them 180 came from electronic database and 1 of them came from other source. 163 of these studies were eliminated after finding duplicates and reviewing the title and abstract. After full-text review, only 7 studies were ultimately included in our analysis.

Characteristics of Included Studies The basic characteristics of the included studies were described in Table 1. Among these seven studies, three of the trials were performed in USA [3,23,24]; the other four were performed in UK [26], Italy [25], Austria [19] and Denmark [20], respectively. The

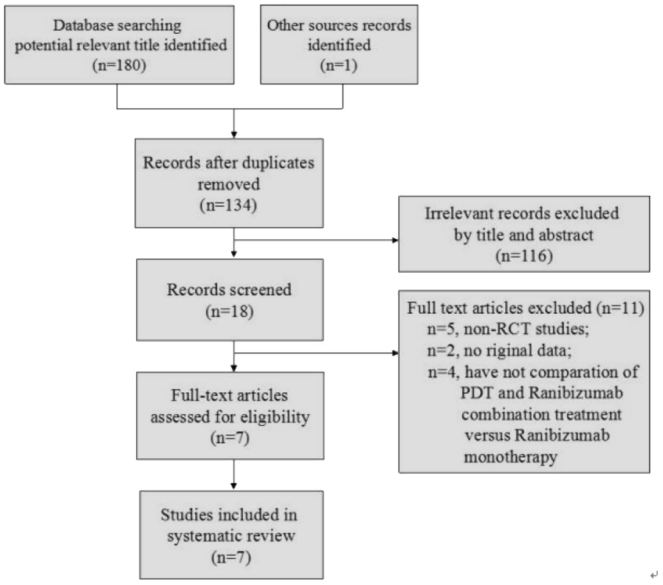

Figure 1 Flowchart showing the number of studies evaluated and excluded from the systematic review.

age of patients varied from 50 to 95y. All of the seven studies used VA and CRT indicators to assess the effect of treatment on AMD and six referred to adverse events. However, clinical heterogeneity could be seen in several areas such as dosage of verteporfin or treatment protocols. In five studies, the intervention of combination groups were 50 J/cm^2 standard fluence (SF) verteporfin PDT and 0.5 mg Ranibizumab, while the PDT was 20% and 40% of standard fluence in Chen's study[23] and was 50% in William's study[24]. Moreover, the duration of follow-up was 12mo in six studies except the study by Giustolisi *et al* [25], which continued only 6mo.

Methodological Quality of Included Studies All the included studies were assessed for methodological quality according to the Jadad score. Among the seven studies, score of two trials [3,20] were 5, score of two other trials [19,26] were 4, and score of remaining three trials [23-25] were 2. Importantly, four of the studies possess high quality[3,19,20,26].

Estimation of Outcomes

Changes in mean BCVA at month 12 *vs* baseline As functional outcome measure, visual acuity (va) was the most important indicator in evaluating efficacy. We compared the changes in mean BCVA extracted from 4 studies whose follow-up was 12mo [3,19,20,26] *vs* the relevant baseline. The pooled results revealed that the ranibizumab monotherapy group had a better visual acuity compared with the combination group, and there was a significant difference (WMD, -2.61; 95% CI, -5.08 to -0.13; P=0.04). Nevertheless, the clinical heterogeneity could be found in the Krebs' study[19]. To exclude the clinical heterogeneity among studies, we removed the Krebs' study to apply the sensitivity analysis and found that the result of statistical analysis was insignificant (WMD, -2.29; 95% CI, -4.81 to 0.23; P=0.07) (Figure 2).

Table 1 Study characteristics of the included seven randomized controlled trials

Study	Country of publication	Major inclusion criteria	Major exclusion criteria	M/F	Mean age (a)	Number of eyes	Intervention groups	Follow-up (months)	Jadad score
Williams 2012[24]	USA	Untreated subfoveal neovascular AMD	Pigment epithelial detachments greater than 50% of the total lesion size	N/R	Group1: 79.1 Group2: 79.3	Group1:27 Group2:29	Group1: ranibizumab (monthly for 3mo then as required) Group2: ranibizumab (with retreatment as required)+half-fluence PDT(25 J/cm^2)	every month in 12mo	2
Vallance 2010[26]	UK	BCVA:between 24 and 73 letters	Patient who had previously received any other treatment for neovascular AMD	N/R	N/R	Group1:9 Group2:9	Group1: ranibizumab (0.5 mg; monthly for 3mo then as required)+SF PDT (50 J/cm^2) Group2: ranibizumab(0.5 mg; monthly for 3mo then as required)+sham PDT	every month in 12mo	4
Giustolisi 2011[25]	Italy	BCVA≥10 letters; classic subfoveal CNV lesions due to AMD; age≥55y	Previous treatment with bevacizumab or ranibizumab or PDT	Group1:9/8 Group2:15/15	Group1:71.24 Group2:70.57	Group1:17 Group2:30	Group1: ranibizumab (0.5 mg; with retreatment as required)+ SF PDT (50J/cm^2) Group2: ranibizumab (0.5 mg; monthly for 3mo then as required)	every month in 6mo	2
Krebs 2013[19]	Austria	Age>50y; predominantly classic lesions and occult or minimally classic lesions with evidence of recent disease progression.	Have a BCVA<33 letters in both eyes; Prior treatment in the study eye for nAMD	N/R	All:78.86±7.83 Group1:77.71±8.87 Group2:80.25±6.32	Group1:22 Group2:19	Group1: ranibizumab (0.5 mg;monthly for 3mo then as required) Group2: ranibizumab (0.5 mg;monthly for 3mo then as required)+SF PDT(50J/cm^2)	every month in 12mo	4
Chen 2010[23]	USA	Age≥55y; visual acuity between 20/32 and 20/320 by ETDRS refraction	N/R	All patients are male	All:66~80y	Group1:2 Group2:2 Group3:3	Group1: ranibizumab (0.5 mg; monthly for 3mo then as required)+sham PDT Group2: ranibizumab (0.5 mg;monthly for 3mo then as required)+20%fluence PDT(10 J/cm^2) Group3: ranibizumab (0.5 mg; monthly for 3mo then as required)+40% fluence PDT (20 J/cm^2)	every month in 12mo	2
Larsen 2012[20]	Denmark	Age≥50y; BCVA of the stuty eye between 73 and 24 letters	Patient who had received prior treatment for neovascular AMD in the study eye;retinal pigment epithelium tear	Group1: 44/78 Group2: 59/74	Group1:76.8±7.7 Group2:75.5±7.4	Group1:122 Group2:133	Group1: ranibizumab (0.5 mg; monthly for 3mo then as required)+PDT (50 J/cm^2) Group2: ranibizumab (0.5 mg;monthly for 3mo then as required)+sham PDT	every month in 12mo	5
Kaiser 2012[3]	USA	BCVA:between 73 and 24 letters; maximum permitted linear dimension of the total lesion was 5400 μm	Received prior treatment for neovascular AMD in the study eye; retinal pigment epithelium tear	N/R	N/R	Group1:103 Group2:105 Group3:110	Group1: ranibizumab (0.5 mg; monthly for 3mo then as required)+SF PDT (50 J/cm^2) Group2: ranibizumab (0.5 mg;monthly for 3mo then as required)+RF PDT (25 J/cm^2) Group3: ranibizumab (0.5 mg;monthly for 12mo)	every month in 12mo	5

SF PDT: Standardized fluence PDT; BCVA: Best corrected visual acuity; nAMD: Neovascular age-related macular degeneration; N/R: Not reported; ETDRS: Early treatment diabetic retinopathy study; CNV: Choroidal neovascularization; RF PDT: Reduced fluence PDT.

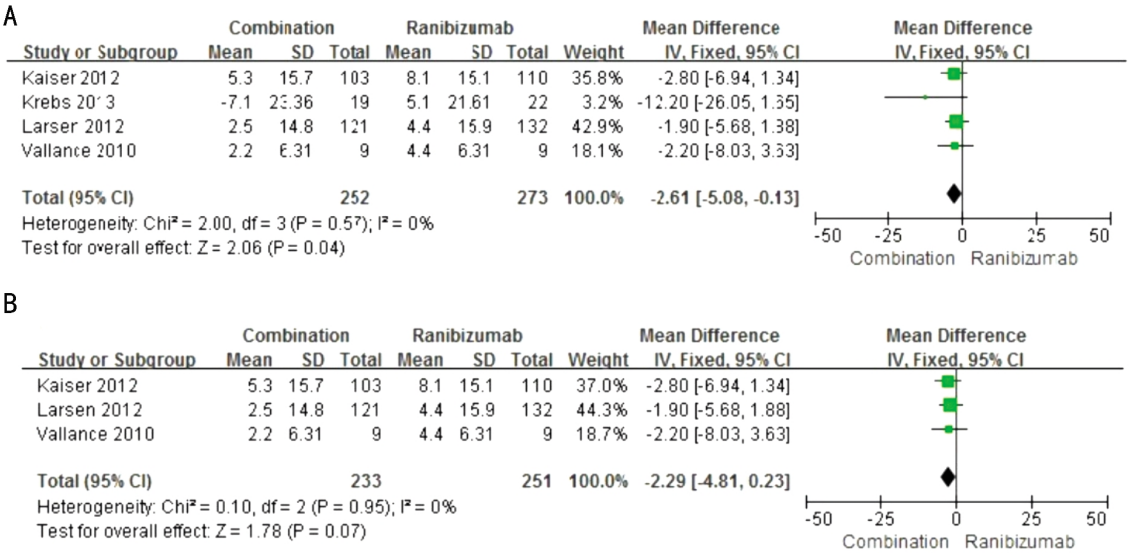

Figure 2 Forest plot showing change in mean BCVA at month 12 *vs* baseline A: Krebs' study included; B: Krebs' study excluded.

Thus, we concluded that it was the clinical heterogeneity that altered the statistical result. In Krebs's study, there was no sham PDT in the ranibizumab monotherapy group, so the blinding was not perfect. Besides, the Krebs's study excluded patients whose BCVA was less than 33 letters, while other three studies' inclusion criteria was between 24 and 73 letters for BCVA. Thus, the BCVA baseline in Krebs' study was better.

Three studies have shown significant clinical heterogeneity, so the quantitative analysis excluded these studies [23-25]. The basic characteristics of the three studies were shown in Table 1. The alterations in mean BCVA *vs* the relevant baseline were

Table 2 Changes in mean BCVA and CRT *vs* relevant baseline extracted from the other three studies

	Williams 2012 (12mo)[24]		Giustolisi 2011 (6mo)[25]		Chen 2010 (12mo)[23]		
	ranibizumab	half-flunce PDT (25 J/cm^2)+ranibizumab	ranibizumab	SF PDT (50 J/cm^2)+ ranibizumab	ranibizumab	20%-flunce PDT (10 J/cm2)+ranibizumab	40%-flunce PDT (20 J/cm^2) +ranibizumab
mean BCVA change	9.9	2.6	6.41	4.73	0.5	-7.67	-10
SD	N/R	N/R	13.34	13.18	0.5	8.81	0
mean CRT change (μm)	-92.5	-106.7	-81	-113	-28.5	-8.67	-60
SD	111.26	94.12	N/R	N/R	3.54	90.79	0

BCVA: Best corrected visual acuity; CRT: Central retinal thickness; N/R: Not reported; SF PDT: Standard flunce PDT.

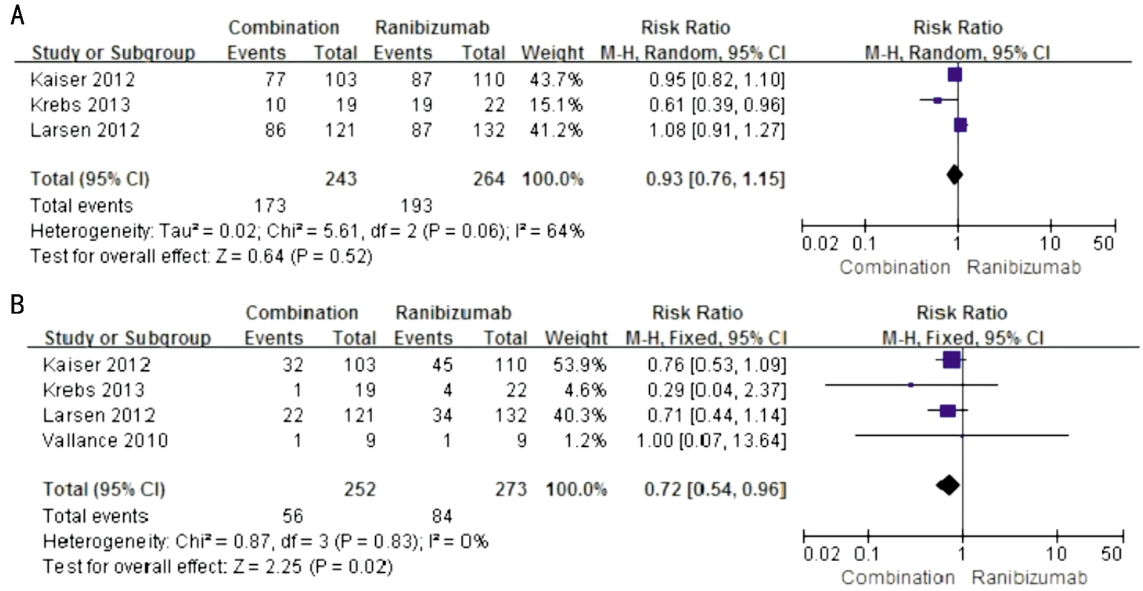

Figure 3 Forest plot showing patients gained more than 0 line and 3 lines at month 12 A: patients gained more than 0 line at month 12; B: patients gained more than 3 lines at month 12.

shown in Table 2.

Number of patients gained more than 0 line at month 12 We extracted the number of patients who gained more than 0 line at month 12 and found that there was statistical heterogeneity among studies for this measure of effect (P=0.06, I^2=64%). So we used random effect model. The pooled RR showed there was no significant difference among combination group *vs* ranibizumab monotherapy group (RR, 0.93; 95% CI, 0.76 to 1.15, P=0.52) (Figure 3A).

Number of patients gained more than 3 lines at month 12 We also extracted the number of patients who gained more than 3 lines at month 12. The statistical heterogeneity was found that there was no significant difference (P=0.77, I^2=0%). The pooled RR showed that the proportion of patients who gained more than 3 lines at the ranibizumab monotherapy group was higher than that of the combination group and the statistical difference was significant (RR, 0.72; 95% CI, 0.54 to 0.95; P=0.02) (Figure 3B).

Central retinal thickness CRT is the most important anatomical change in AMD treatment. We compared the change in mean CRT at month 12 *vs* baseline extracted from 4 studies [3,19,20,26] (Figure 4). The pooled results reveal that there was no significant CRT reduction in the combination group in comparison with ranibizumab monotherapy group at 12mo follow-up, although combination group tended to have greater reduction (WMD, - 4.13 μm; 95% CI, -25.88 to 17.63, P=0.71). The change in mean CRT *vs* baseline extracted from the other three studies[23-25] was shown in Table 2 (Figure 4).

Adverse events recorded at month 12 In Vallance's study, there was no adverse events in both groups, and there was no reports about adverse events in Krebs' study [19,26]. Ocular adverse events and systematic adverse events were both reported in the Larsen's and Kaiser's studies [3,20]. Further, we compared the number of eye pain, endophthalmitis, hypertension, and arterial thromboembolic events in the combination group and ranibizumab monotherapy group and found none of them had significant difference between the combination group and ranibizumab monotherapy group (Figure 5). All adverse events reported in the Larsen's and Kaiser's studies were shown in Table 3. Overall, the incidence of serious adverse events (endophthalmitis, Macular hole) was very low.

Besides the four studies above-mentioned, the other three studies did not report adequate data about adverse events[23-25].

Number of ranibizumab retreatment at month 12 Due to the inadequate data of ranibizumab retreatment, the meta-analysis could not be assessed. The data extracted from

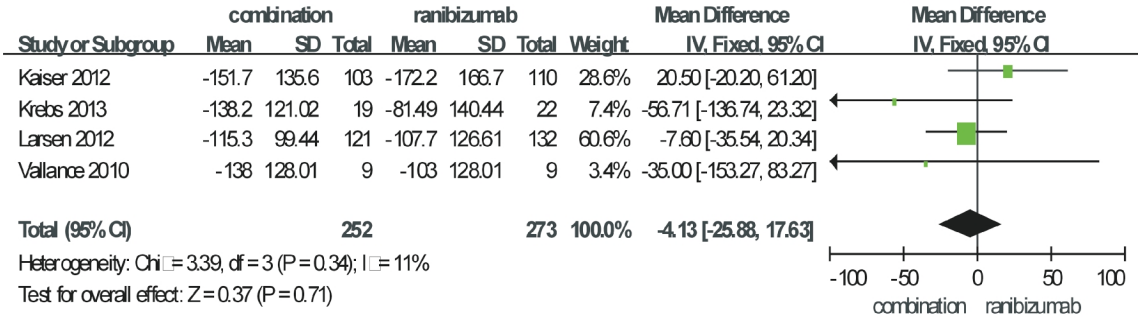

Figure 4 Forest plot showing change in mean CRT at month 12 *vs* baseline.

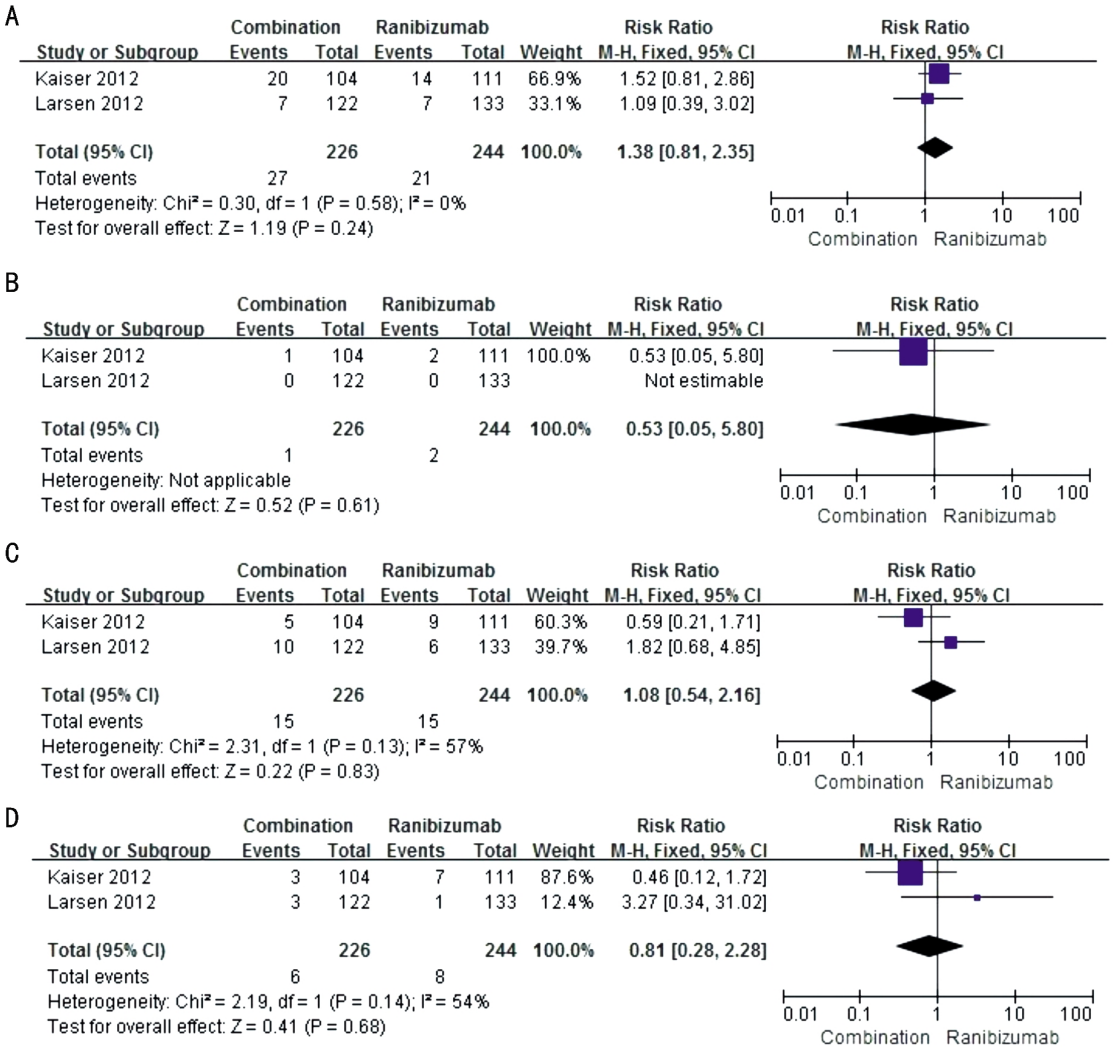

Figure 5 Forest plot showing number of patients with eye pain, endophthalmitis, hypertension and arterial thromboembolic events at month 12 A: number of patients with eye pain; B: number of patients with endophthalmitis; C: number of patients with hypertension; D: number of patients with arterial thromboembolic events.

four studies were shown in Table 4. In Vallance's study, the numbers of ranibizumab retreatment were both 1.3 injections in two groups [3,19,20,26]. Nevertheless, the four studies' general tendency shows a reduction of ranibizumab retreatment numbers in combination group (mean 1.95 injections) compared with the ranibizumab monotherapy group (mean 4.39 injections).

DISCUSSION

The purpose of our systematic review of existing data is to to compare the efficacy and safety of combination of PDT with intravitreal ranibizumab versus ranibizumab monotherapy. To our knowledge, this is the first systematic review comparing these two treatments.The results of the systematic review show that the ranibizumab monotherapy group had a better mean BCVA change compared with the combination group. However, after removing the Krebs' study [19] ,we found that the statistical difference became insignificant. Owing to a better BCVA baseline in Krebs' study, we conclude that PDT treatment may maintain lower visual acuity. Moreover, Krebs' study had an imperfect blinding, so it could not avoid

Table 3 The main ocular adverse events and systemic adverse events reported

Event	Combination (*n*=245)		Ranibizumab (*n*=266)	
	Number of reported case	Incidence (%)	Number of reported case	Incidence (%)
Serious Ocular Adverse Events				
Endophthalmits	1	0.41	2	0.75
Macular hole	1	0.41	0	0
Other Ocular Adverse Events				
Eye pain	27	11.02	21	7.89
Conjunctival hemorrhage	14	5.71	24	9.02
Ocular hyperemia	14	5.71	16	6.02
Inraocular pressure increased	8	3.27	7	2.63
Reduced visual acuity	17	6.94	14	5.26
Blepharitis	5	2.04	4	1.5
Lacrimation increased	4	1.63	9	3.38
Myodesopsia	2	0.82	8	3.01
Photopsia	1	0.41	5	1.88
Maculopathy	9	3.67	0	0
Retinal hemorrhage	10	4.08	6	2.26
Retinal edema	7	2.86	0	0
Non-ocular Adverse Events				
Hypertension	15	6.12	15	5.64
Arterial thromboembolic	6	2.45	8	3.01

Table 4 Number of ranibizumab retreatment at month 12

	Krebs *et al*[19]		Vallance *et al* [26]		Larsen *et al* [20]		Kaiser *et al*[3]	
	Combination	Ranibizumab	Combination	Ranibizumab	Combination	Ranibizumab	Combination	Ranibizumab
Mean	1.7	3.6	1.3	1.3	1.9	2.2	2.2	7.6
SD	N/R	N/R	N/R	N/R	1.98	1.97	N/R	N/R

N/R: Not reported.

the performance bias among the study. Meanwhile, we also noted that both combination treatment group and ranibizumab monotherapy group can efficiently stabilize visual acuity (*i.e.* gained more than 0 line) at month 12 (Figure 3A). Using the criteria of gaining visual acuity more than 3 lines, the ratio of the patients who gained more than 3 lines in ranibizumab monotherapy group was more than that in combination treatment group (Figure 3B), indicating that patients treated with ranibizumab monotherapy may get more visual acuity improvement. However, no significant CRT reduction was found in the combination treatment group in comparison with the ranibizumab monotherapy group at month 12, yet combination treatment group had greater potent to reduce the CRT compared with monotherapy group. Thus, it seems that the greater reduction of CRT means less leakage of the retina and less retinal edema, and thus the visual acuity of patients could maintain stability for longer time.

Three of seven studies mentioned-above carried out RCT and further performed the comparison of reduced fluence PDT combined with ranibizumab *vs* ranibizumab monotherapy[23-25]. Reduced fluence PDT may decrease choroidal hypoperfusion, vascular leakage, inflammation and the up-regulation of VEGF that is associated with standard fluence PDT [2]. In Williams' study [24], there was a tendency toward less ranibizumab injections and worse visual acuity in the combination group compared with the ranibizumab monotherapy group, but there was no significant statistical differences. This study was limited by the small number of patients and the lack of masking. The Kaiser's study [3] compared the reduced and standard fluence PDT combined with ranibizumab *vs* ranibizumab monotherapy, respectively, and the results indicate no differences about the frequency of retreament and the improvement of visual acuity. These results can not absolutely support the addition of reduced fluence verteporfin PDT to ranibizumab treatment, and it needs larger studies to determine whether the addition of reduced fluence PDT causes better changes in outcomes.

The blockage effect of ranibizumab on VEGF is only temporary, and an added PDT may lead to a more permanent and rapid occlusion of CNV. On the other hand, the application of PDT alone can up-regulate VEGF and result in recurrences of CNV and the need of repeat treatments, but ranibizumab may counteract this proangiogenetic effect of

PDT. In this case, the combination therapy has its merits. Different pathways of function might offer a collaborative effect, especially on the number of needful retreatment. In our analysis, the combination treatment group had the tendency to reduce the number of ranibizumab retreatment compared with the ranibizumab monotherapy group. In consideration of the efficacy and the cost of retreatmnet and follow-up, combination treatment might be a cost-effective option for the treatment of neovascular AMD compared with monotherapy.

Because of the worse visual outcome, the combination of either reduced or standard fluence PDT with ranibizumab cannot replace the ranibizumab monotherapy routinely in clinic application. However, intravitreal injections of ranibizumab may be linked with an increased risk of adverse events, especially endophatholmitis and arterial thromboembolic events. Although the incidence of endophthalmitis or arterial thromboembolic events is very low, this risk could rise with the number of injections increased in two years and more [27,28]. In some patients who have already suffered a myocardial infarct or a stroke and who are inconvenient to monthly follow-up for injections, combination treatment might be necessary to reduce the number of injections; meanwhile, it could also eliminate the risk of the progress of neovascular AMD. Furthermore, less number of injections of ranibizumab could reduce burden to the patient.

In conclusion, our analysis cannot demonstrate any statistically significant advantage of clinical efficacy and safety between the combination of ranibizumab with PDT and ranibizumab monotherapy for neovascular AMD, but the potential remains for dual therapy to afford some benefit over anti-VEGF monotherapy. Our systematic review includes seven RCT studies, and most of them are high quality studies. However, the small number of studies, small sample size of patients and the different study designs prevent the extraction of more data about the efficacy and safety of combination treatment *vs* ranibizumab monotherapy for AMD. Well-designed, large scale and high-quality RCTs are needed for stronger evidence and more information about the adverse events should also be provided in farther trials.

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