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Comparison of Aflibercept and Ranibizumab on Functional and Morphological Outcome in Exudative Age-Related Macular Degeneration

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Abstract

Background: Exudative, or "wet" age-related macular degeneration (wAMD), characterized by choroidal neovascularization and consequent accumulation of subretinal fluid, is the leading cause of visual loss in elderly patients in Western countries. **Objective:** To compare the effectiveness of aflibercept vs. ranibizumab for treatment-naive wAMD patients in the real world. **Methods:** PubMed, Web of Science and Cochrane Library were searched to compare aflibercept with ranibizumab. 21 studies with a total of 13,004 eyes were selected and assessed in this meta-analysis. **Results:** Compared to ranibizumab, aflibercept was more effective in improving best-corrected visual acuity (BCVA) at 12 months (WMD: −0.04; 95% CI: −0.07 to 0.00; p = 0.04). At 3 months, aflibercept was superior to ranibizumab in reducing central retinal thickness in patients with worse baseline BCVA (WMD: −36.19; 95% CI: −71.47 to −0.92; p = 0.04), reducing subfoveal choroidal thickness in patients with better baseline BCVA (WMD: −12.67; 95% CI: −21.33 to −4.02; p = 0.004), reducing height of subfoveal pigment epithelial detachment (WMD: −43.88; 95% CI: −73.88 to −13.87; p = 0.004) and improving the incidence of "dry macula" occurrence (OR: 2.26; 95% CI: 1.33 to 3.82; p = 0.003). **Conclusions:** Compared with ranibizumab, aflibercept showed better efficacy in improving morphological changes at 3 months and visual acuity at 12 months post treatment initiation in community clinical setting.

Keywords

Ranibizumab, Aflibercept, Age-Related Macular Degeneration

1. Introduction

Exudative, or "wet" age-related macular degeneration (wAMD), characterized by choroidal neovascularization (CNV) and consequent accumulation of subretinal fluid, is the leading cause of visual loss in elderly patients in the developed countries [1]. The upregulation of vascular endothelial growth factor (VEGF) plays an important role in the abnormal blood vessel growth and neovascularization. Anti-VEGF treatment can prevent further neovascularization and reverse visual loss from wAMD [2]. Currently, two of the most used commonly used drugs are ranibizumab (Lucentis®, Genentech Inc., South San Francisco, CA, USA) and aflibercept (EYLEA® Injection 2 mg, Regeneron, Tarrytown, NY, USA). Both drugs were approved for this use in the US (2006,2011) and by the European Medicines Agency (2007,2012).

Meta-analyses of randomized clinical trials (RCTs) have compared the efficacy between aflibercept and ranibizumab for wAMD [2]-[4]. However, populations and treatment regimens in RCTs may not be representative of those in the real world [5] [6]. "Real-world" treatment conditions were defined as routine clinical practice. They do not involve random assignment but rather observe how patients receive treatment in regular medical settings and the effects of these treatments. "Real-world" study (RWS) typically includes a broader patient population, including those who might be excluded from RCTs. The advantage of RWS is that they can provide information on the effectiveness and safety of treatments in actual application, not just theoretical possibilities. Therefore, the results comparing aflibercept vs. ranibizumab from RCTs may not be replicated in clinical routine practice. To our knowledge, only one meta-analysis of real-world studies has shown that aflibercept and ranibizumab had similar effects on best-corrected visual acuity (BCVA) and central retinal thickness (CRT) in wAMD, and that a lower baseline BCVA might lead to a better visual outcome with the use of aflibercept based on a subgroup analysis of 12-month treatment outcomes [7]. However, a short-term subgroup analysis (at 3-month post treatment initiation) is also valuable, because persistent subretinal and intraretinal fluid could further damage cells in the outer retina, resulting in poor visual long-term prognosis in wAMD. Additionally, more sensitive outcome measures, such as subfoveal choroidal thickness (sfCT), incidence of "dry macula (DM)" and subfoveal pigment epithelial detachment height (sfPEDH), all related to CNV activity, would be beneficial to better estimate treatment efficacy. Therefore, we systemically searched and analyzed observational studies to compare the treatment effect, in terms of BCVA and morphological change related with CNV activity, between aflibercept and ranibizumab for wAMD across different follow-up times and baseline visual acuity.

2. Methods

This meta-analysis was confirmed to the recommendations of the Cochrane Handbook and reported according to the PRISMA reporting guidelines for meta-analysis and systematic review. The PRISMA checklist was provided in

Supplementary Table S1.

2.1. Search Strategy

Online electronic databases (PubMed, Web of Science, and the Cochrane Library) were searched with an end date of August 12, 2024. The following MeSH terms were used in [Title/Abstract]: "Macular Degeneration or Age-Related Macular Degeneration or AMD or ARMD or nAMD", and "ranibizumab or Lucentis", and "aflibercept or Eylea". Additionally, the "related articles" function was used to complement the searches of the reference lists of all retrieved studies.

2.2. Inclusion and Exclusion Criteria

Only observational studies that reported results of comparison between aflibercept monotherapy and ranibizumab monotherapy for wAMD patients with no previous therapy, and that had at least one quantitative outcome of visual function or retinal morphology reported, were included. When multiple published articles described the same population, the most recent or complete report was used. Only studies published in peer-reviewed journals and in English were considered, irrespective of main outcomes, date, region or publication types. Conference papers/abstracts, editorials, letters to authors, reviews, commentaries and news were not included in the review. In addition, journal articles were excluded if they met the following criteria: 1) Follow-up time less than 3 months; 2) Case reports; 3) Pre-clinical studies; 4) Relatively small sample size (less than 20 eyes/group).

2.3. Study Selection

Figure 1 shows a flow chart of the selection process used to identify relevant studies. Data of included studies were extracted and summarized independently by two reviewers (X.W. and C.Y.). Any disagreement was resolved by a third reviewer (J.D.). The main outcomes were BCVA, CRT and sfCT. The other outcomes were incidence of "DM" and sfPEDH.

2.4. Data Collection and Risk of Bias Assessment

Studies were rated for the level of evidence provided according to criteria by the Centre for Evidence-Based Medicine (Oxford, UK). The methodological quality of all cohort studies was assessed by the Newcastle-Ottawa scale (NOS) [8], which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome (Supplementary Table S1). A 10-point scale was used and a score of 0 - 9 was allocated to each study. Two reviewers (X.W. and C.Y.) assessed the quality of the studies. Any discrepancies were resolved by a third reviewer (J.D.). Observational studies achieving a score of seven or more points were considered to be of high quality.

2.5. Data Synthesis and Analysis

All analyses were performed using Review Manager 5.3 (Cochrane Collaboration,

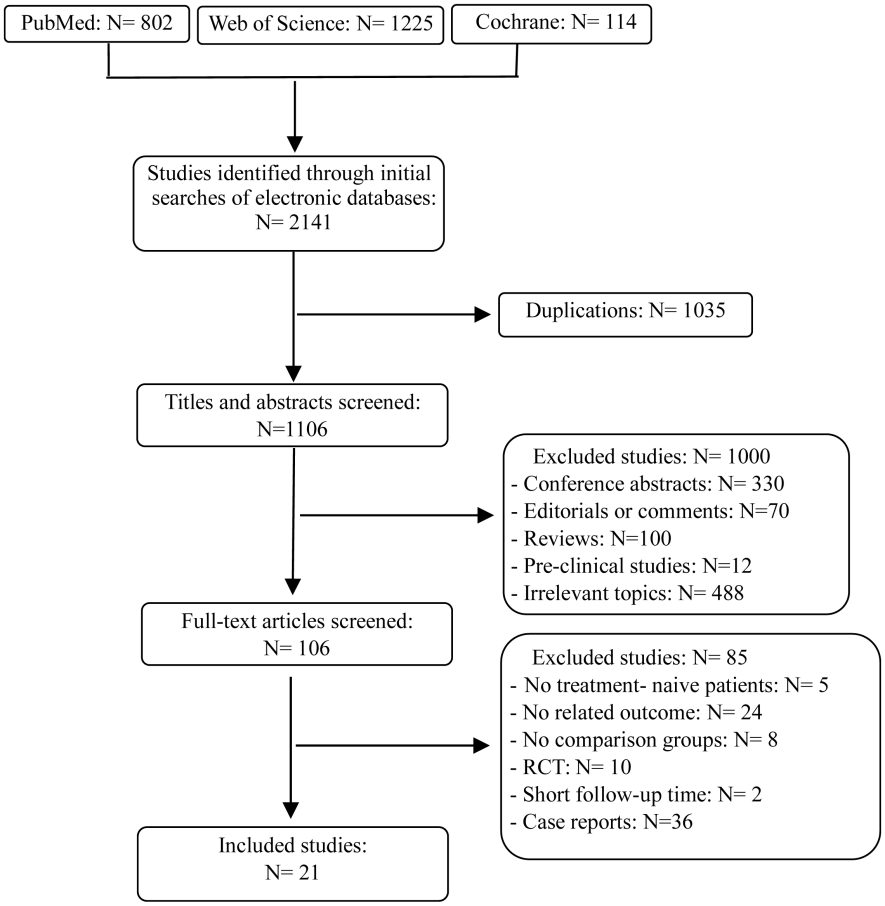

Figure 1. Flow diagram of studies identified, included and excluded.

Oxford, UK). The weighted mean difference (WMD) and odds ratio (OR) were used to analyze continuous and dichotomous variables, respectively. All results were reported with 95% confidence intervals (CIs). If continuous data were presented as means and range values, the standard deviation (SD) were calculated using the technique described by Hozo *et al.* [9]. An OR of less than 1 favored the Aflibercept group. Heterogeneity between studies was assessed by the χ^2 and I^2 statistic. The random-effects model was used if the p value was less than 0·1, otherwise, the fixed-effects model was reported. A two-tailed $p < 0.05$ was considered significant. Begg's test and funnel plot analyses were used to assess the publication bias.

Subgroup analyses were performed to compare BCVA at baseline of less than or more than 0.6 logMAR (55 ETDRS letters) based on a recent study which reported that BCVA improvement was different between eyes with a baseline acuity at more than 0.6 logMAR vs. eyes with lower baseline BCVA [7].

3. Results

3.1. Included Studies

As a result of the literature search, 802, 1225 and 114 studies published in English in PubMed, Web of Science and Cochrane, respectively, were identified. After

checking for duplications, 1035 studies were kept for stepwise review. Of these studies, 106 articles that were relevant to the study topic were retained for full text review. Finally, after full-text review of these 106 articles, 21 studies met the inclusion criteria [10]-[30]. Agreement between the two reviewers was 95% for study selection and 95% for quality assessment of trials after examination of references listed for studies. The literature search process was summarized in **Figure 1**.

3.2. Characteristics of Included Studies

There was one prospective study [28] and the remaining studies were retrospective. In total, there were 6832 eyes in aflibercept and 6172 eyes in ranibizumab groups, respectively. Follow-up time varied from 1 to 24 months, the majority of studies had a 3-months (13, 61.9%) and 12-months (14, 66.7%) follow-up after the initial treatment. Only two studies have reported the change of BCVA and CRT at 24-months follow-up, however, they have both been analyzed in a previous meta-analysis and are not reported here [7]. Detailed information about follow-up and regimen was summarized in Supplementary **Table S2**.

Quality assessment showed one trial with a score of 5, which was a relatively lower score compared to the other studies [11]. The quality of remaining studies was relatively high, with an average score of 7.9 (Supplementary **Table S3**). Two articles recorded the same population with different outcomes reported, therefore, both studies were included [16] [17].

3.3. Main Outcomes

3.3.1. Mean Change in BCVA

The measured BCVA values were converted to logarithm of the minimum angle of resolution (logMAR) units. Effects of aflibercept and ranibizumab on mean BCVA change were compared at two different time points of follow-up (3 months and 12 months). Although BCVA change has been compared in a previous meta-analysis [7], more accurate results could be obtained in this work with the inclusion of five more studies.

The pooled BCVA change data from 13 studies [10]-[12] [15] [16] [18]-[21] [23] [26] [28] [29] showed no difference in BCVA at 3 months (WMD: −0.01; 95% CI: −0.04 to 0.01; p = 0.42), while the data from 14 studies [13]-[16] [19] [20] [22]-[27] [29] [30] showed borderline significance in favor of aflibercept (WMD: −0.04; 95% CI: −0.07 to 0.00; p = 0.04) at 12 months post initiation of treatment (**Figure 2**). Due to high heterogeneity observed, a random-effects model was used at 3 months (χ^2 = 19.73, df = 12, p = 0.07; I^2 = 39%) and at 12 months (χ^2 = 33.91, df = 13, p = 0.001; I^2 = 62%). No publication bias was detected by Begg's test for the comparison effects on BCVA at 3 months (p = 0.583; **Figure 3(A)**) and at 12 months (p = 0.381; **Figure 3(B)**). At one year follow-up visit, this outcome differs from the same measure reported in a previous meta-analysis which showed no significant difference [7], most likely due to an increased number of included studies (fourteen in the current one vs. eleven in the previous one). However,

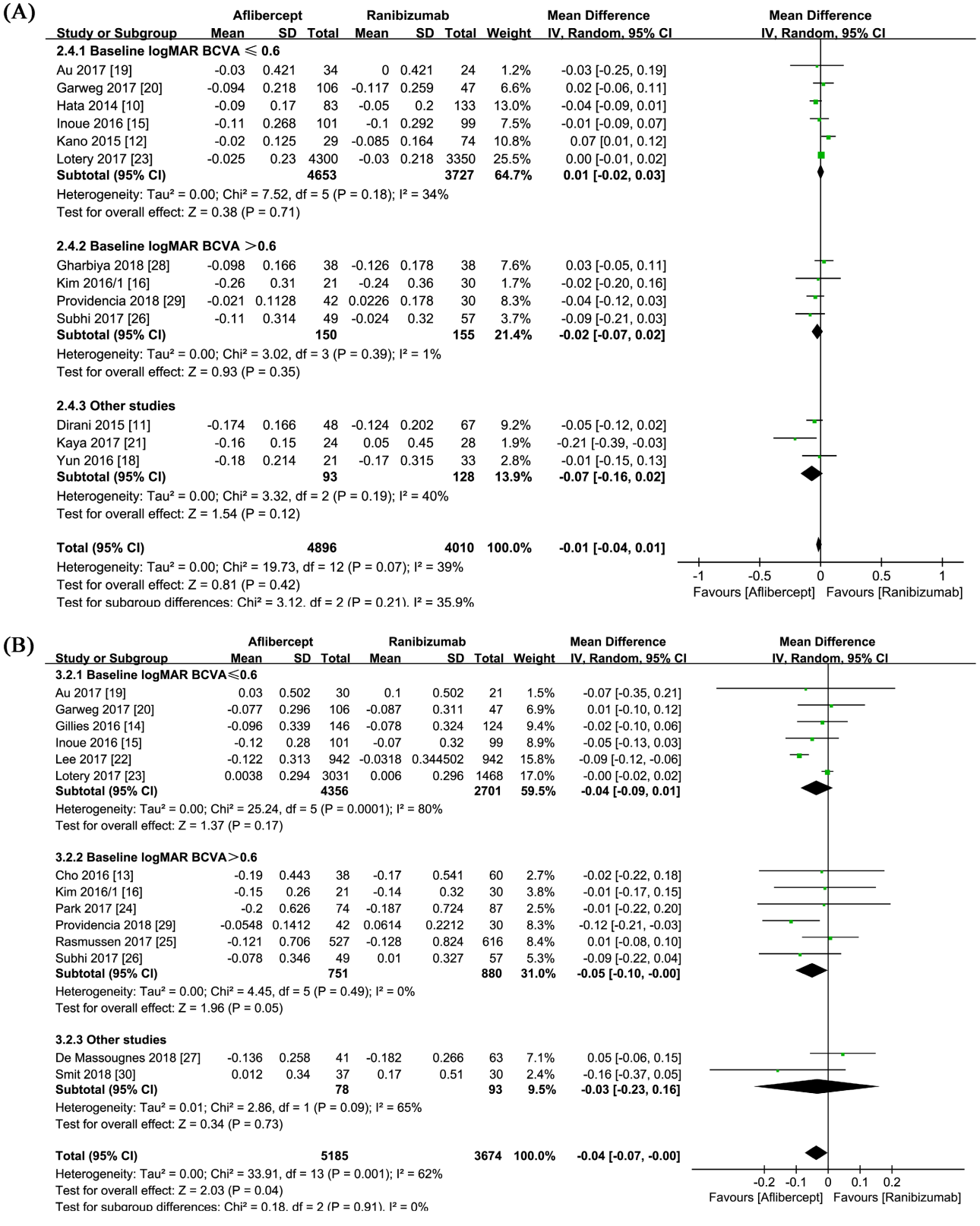

Figure 2. Differences in BCVA (logMAR) changes between aflibercept and ranibizumab treatment at 3(A) and 12(B) months. BCVA: best-corrected visual acuity; logMAR: logarithm of minimum angle of resolution.

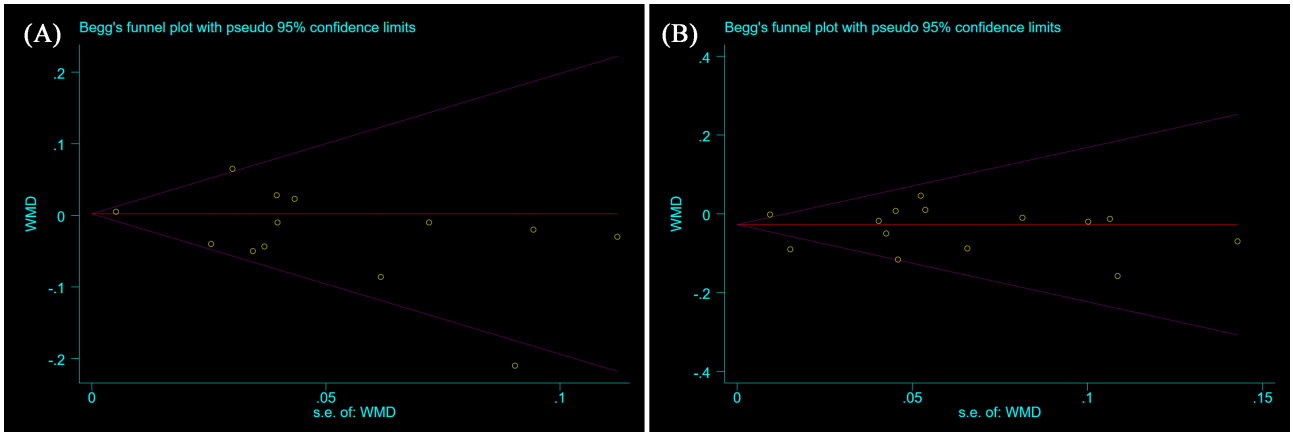

Figure 3. Beggs's funnel plot for assessing publication bias of BCVA changes at 3 months (A) and 12 months (B).

high heterogeneity among studies indicated a relatively weak advantage in favor of aflibercept at 12 months.

3.3.2. Mean Change in CRT

The CRT was defined as the distance between the inner surface of the neurosensory retina and the retinal pigment epithelium (RPE) in the central retina. Compared with the previous meta-analysis, two more studies [28] [29] reported the treatment effects of CRT thinning between aflibercept and ranibizumab in routine clinical practice. The two pooled analyses from nine [10] [12] [15] [16] [19] [20] [26] [28] [29] and eight [13] [15] [16] [19] [20] [24] [26] [29] studies showed no significant difference in CRT change between two groups at the 3 months(WMD: −2.93; 95% CI: −20.10 to 14.25; p = 0.74) and 12 months (WMD: 2.64; 95% CI: −18.55 to 23.83; p = 0·81) visit, respectively. No heterogeneity was observed among the studies at 3months (χ^2 = 8.39, df = 8, p = 0.4; I^2 = 5%) and 12 months (χ^2 = 4.40, df = 7, p = 0·73; I^2 = 0%) (**Figure 4**). No publication bias was detected by Begg's test for the comparison effects on CRT at 3 months (p = 0.466) and at 12 months (p = 0.174).

3.3.3. Mean Change in sfCT

The sfCT was defined as the vertical distance between Bruch's membrane and the chorioscleral interface. Six studies [10] [12] [17] [18] [21] [28] including 741 eyes assessed sfCT change at 3 months of follow-up. Despite some tendency for more pronounced thinning in sfCT of aflibercept group, the analysis showed no significant difference between the two groups (WMD: −8.98; 95% CI: −19.38 to 1.43; p = 0·09), with significant heterogeneity among studies (χ^2 = 30.68, df = 5, p < 0.0001; I^2 = 84%) (**Figure 5**). No publication bias was detected by Begg's test (p = 0.707).

Subgroup analysis

Subgroup analyses performed by Zhang *et al.* have been shown that lower baseline BCVA (<0.6 logMAR) might lead to a better visual outcome with the use of aflibercept at 12 months [7]. However, a subgroup analysis of 3-month post

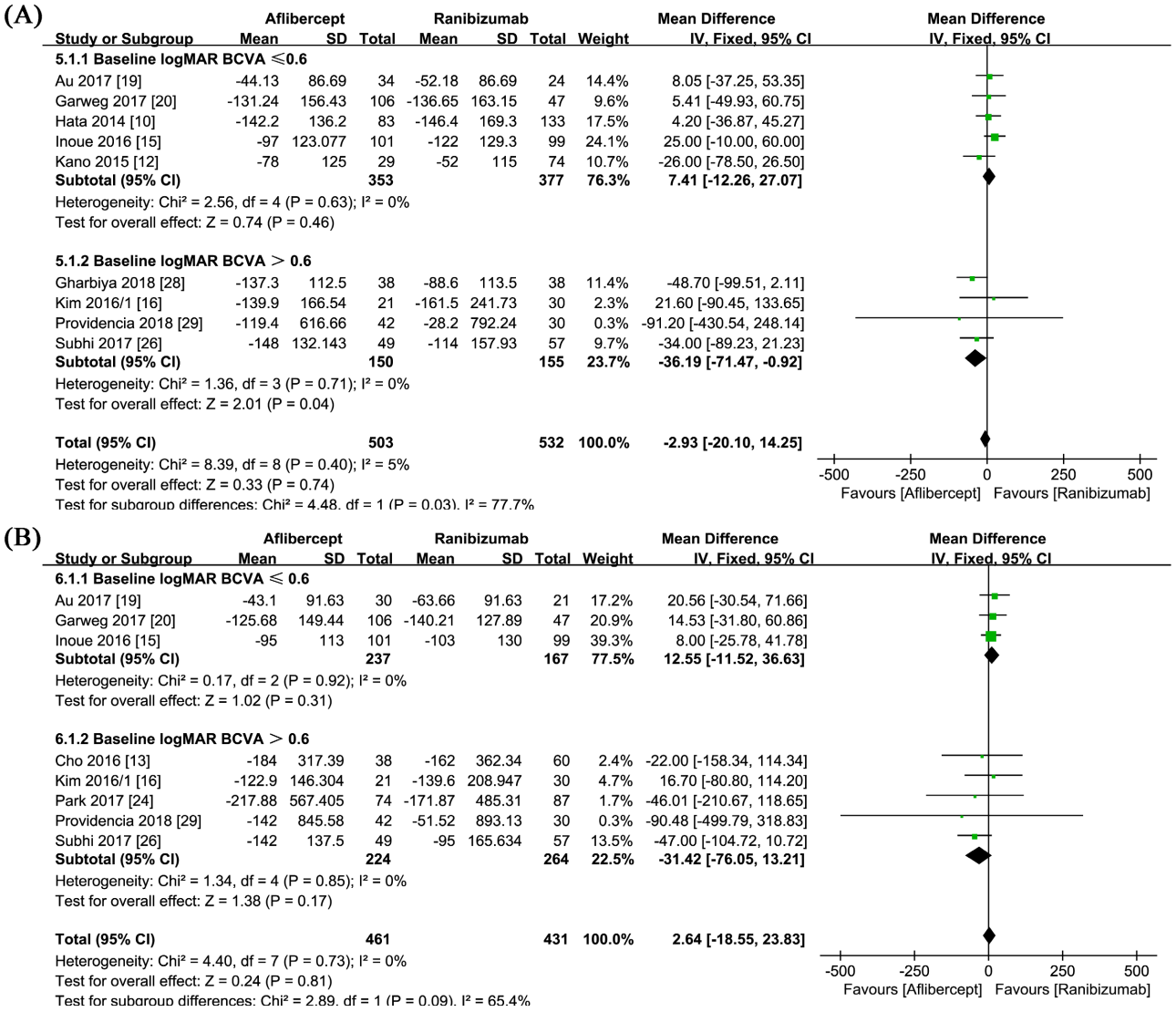

Figure 4. Differences in CRT changes between aflibercept and ranibizumab injection at 3(A) and 12(B) months. CRT: central retinal thickness.

treatment initiation could be also valuable. Therefore, we performed subgroup analyses based on both 3-month and 12-month treatment outcomes for different baseline BCVA levels.

In terms of BCVA improving, there was no significant difference either at 3 months (WMD: 0.01; 95% CI: −0.02 to 0.03; p = 0.71) or 12 months (WMD: −0.04; 95% CI: −0.09 to 0.01; p = 0.17) between the two groups for baseline BCVA better than 0.6 logMAR. For baseline BCVA worse than 0.6 logMAR, no significant difference was observed in 3 months (WMD: −0.02; 95% CI: −0.07 - 0.02; p = 0.35), but a borderline significant difference in favor of aflibercept was observed for BCVA change at one year post treatment (WMD: −0.05; 95% CI: −0.10 to 0.00; p = 0.05).

In terms of CRT thinning, no significant difference at 3 months (WMD: 7.41; 95% CI: −12.26 to 27.07; p = 0.46) and 12 months post treatment (WMD: 12.55;

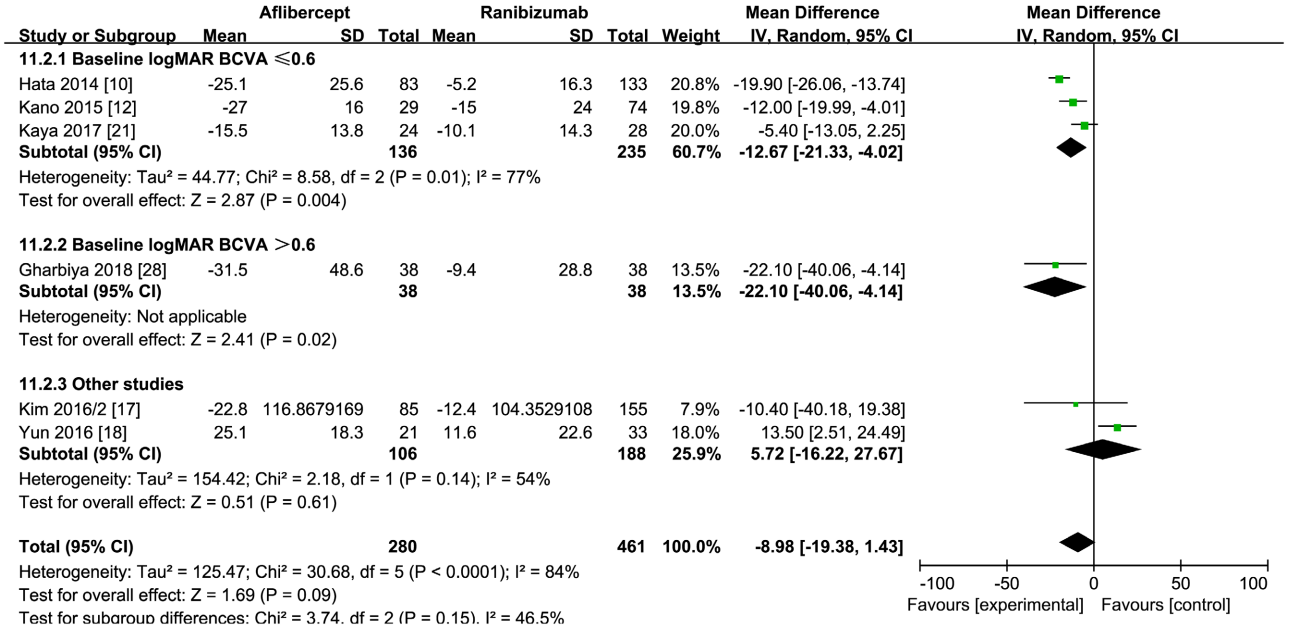

Figure 5. Differences in sfCT change between aflibercept and ranibizumab at 3 months. sfCT: subfoveal choroidal thickness.

95% CI: −11.52 to 36.63; p = 0.31) was observed in eyes with baseline BCVA better than 0.6 logMAR. When the eyes with a baseline BCVA worse than 0.6 logMAR was compared, no significant difference was observed at one year post treatment (WMD: −31.42; 95% CI: −76.05 to 13.21; p = 0.17), but a significant difference in favor of aflibercept in CRT change at 3 months follow-up (WMD: −36.19; 95% CI: −71.47 to −0.92; p = 0.04).

In terms of sfCT thinning, two studies showed that aflibercept was slightly superior in patients with baseline BCVA better than 0.6 logMAR (WMD: −12.67; 95% CI: −21.33 to −4.02; p = 0.004). Only one study reported change in sfCT in eyes with relatively worse baseline BCVA, which made it impossible to perform analysis for this morphological parameter.

3.4. Other Outcomes

3.4.1. Incidence of "DM"

The post-treatment incidence of complete resolution of the accumulation of intraretinal or subretinal fluid (referred to as "DM") was evaluated. Pooling the data from three studies [10] [16] [28] we assessed the incidence of "DM" in 343 eyes after a treatment course of 3 months. The eyes in aflibercept-treated group showed a higher incidence of "DM" compared to the ranibizumab-treated group (OR: 2.26; 95% CI: 1.33 to 3.82; p = 0.003). No significant heterogeneity was observed in the included studies (χ^2 = 2.64%, df = 2, p = 0.27; I^2 = 64%) (Table 1). No publication bias was detected by Begg's test (p = 1.00).

3.4.2. Mean Change in sfPEDH

The sfPEDH was defined as the distance between the outer border of Bruch's membrane and the inner border of the RPE at the fovea. Pooling the data assessed

the mean change in absolute thickness of sfPEDH in 274 eyes at 3 months [10] [19] and in 212 eyes at 12 months [19] [24]. Compared to ranibizumab, aflibercept showed to be slightly more effective in reducing sfPEDH by average ~43.9 μm (95% CI: −73.88 to −13.87; p = 0.004) at 3 months, and by ~34.1 μm (95% CI: −76.30 to 8.07; p = 0.11) at 12 months. There was no significant heterogeneity at 3 months (χ^2 = 0.03, df = 1, p = 0·86; I^2 = 0%) and 12 months (χ^2 = 1.96, df = 1, p = 0.16; I^2 = 49%) (Table 1). No publication bias was detected by Begg's test for the comparison effects on sfPEDH at 3 months (p = 1.00) and at 12 months (p = 1.00).

Table 1. Results of meta-analysis comparison of aflibercept and ranibizumab group.

Outcomes of interest	Studies, no.	Aflibercept Eyes, no.	Ranibizumab Eyes, no.	WMD/OR (95% CI)	P value	Study heterogeneity			
						χ^2	df	I^2, %	P value
Main outcomes									
Mean BCVA change at 3 months (logMAR)	13	4896	4010	−0.01 (−0.04, 0.01)	0.42	19.73	12	39	0.07
Mean BCVA change at 12 months (logMAR)	14	5185	3674	−0.04 (−0.07, −0.00)	0.04	33.91	13	62	0.001
Mean CRT change at 3 months	9	503	532	−2.93 (−20.10, 14.25)	0.74	8.39	8	5	0.40
Mean CRT change at 12 months	8	461	431	2.64 (−18.55, 23.83)	0.81	4.40	7	0	0.73
Mean sfCT change at 3 months	6	280	461	−8.98 (−19.38, 1.43)	0.09	30.68	5	84	<0.0001
Other outcomes									
Incidence of "DM" at 3 months	3	142	201	2.26 (1.33, 3.82)	0.003	2.64	2	24	0.27
Mean sfPEDH change at 3 months	2	117	157	−43.88 (−73.88, −13.87)	0.004	0.03	1	0	0.86
Mean sfPEDH change at 12 months	2	104	108	−34.11 (−76.30, 8.07)	0.11	1.96	1	49	0.16

BCVA: best-corrected visual acuity; logMAR: logarithm of minimum angle of resolution; CRT: central retinal thickness; sfPEDH: subfoveal pigment epithelial detachment height; sfCT: subfoveal choroidal thickness; DM: "dry macula"; WMD: weighted mean difference; OR: odds ratio; 95% CI: 95% credible interval.

4. Discussion

This meta-analysis summarizes the results from one prospective and twenty retrospective clinical trials, including 13,004 eyes and comparing visual function and fundus morphology of intravitreal aflibercept vs. ranibizumab group. Previous meta-analysis observed similar effects of both drugs on BCVA and CRT in routine clinical practice [7], a finding which differs from our results. Compared to ranibizumab, aflibercept had similar visual functional benefits in the short term, however, one-year follow-up results showed that aflibercept was slightly more effective,

improving visual acuity by −0.04 logMAR based on our meta-analysis. However, aflibercept had a relatively weak advantage in terms of BCVA improvement in 12 months. High heterogeneity may lead to decrease statistical significance and increase confidence intervals, which affected the precision of judgment on the results. Therefore, there was a possibility that the advantage of aflibercept in BCVA improvement at 12 months was underestimated. Although the two drugs had comparable effects on the magnitude of CRT reduction at both 3 and 12 months, interestingly, in patients with lower BCVA (logMAR worse than 0.6), aflibercept decreased CRT more significantly than ranibizumab after 3 months of the initial injection. In the short term (3 months), anti-VEGF therapy could promote CRT thinning via reducing CNV leakage. After 3 months of the initial injection, aflibercept decreased CRT more significantly than ranibizumab due to the advantage of molecular structure and pharmacokinetics. However, CNV fibrosis leads to a reduction in this advantage in CRT thinning during long-term treatment.

Choroidal thickness in the macula is typically influenced by the status of the choroidal capillary permeability, which is associated with the presence of an active CNV in patients with wAMD. In terms of sfCT thinning, our meta-analysis showed no significant difference between the two treatment groups after 3-month treatment regardless of the baseline visual acuity level. However, the results of our subgroup analysis showed that aflibercept was superior to ranibizumab in decreasing sfCT for patients with better baseline BCVA (logMAR better or equal 0.6) at 3 months. The average difference in thinning of ~12.7 μm between two groups could also be considered clinically significant as it translates to ~4.5% difference in thickness, assuming ~278 μm average sfCT. For patients with worse baseline BCVA, it was reported that aflibercept was also more effective in sfCT thinning than ranibizumab, however, subgroup analysis was not feasible because only one study reported results [28]. Overall, these findings suggest that aflibercept has the advantage in terms of sfCT normalization in the short term.

Although normalization or decrease towards normalization of CRT has been the basis for retreatment strategies, the outcome of "DM" status is the most desired treatment result in the management of wAMD. In the present meta-analysis, aflibercept showed a higher rate of "DM" appearance (82% vs. 68%) at 3 months, while comparable data were not available at one-year follow-up. This result indicates that aflibercept is more beneficial to improve rapidly exudative retinal changes compared to ranibizumab in wAMD. Furthermore, sfPEDH is considered also a marker of disease severity and predictor of vision loss. Although only two studies reported sfPEDH change were available at different follow-up times, meta-analysis was performed to better understand the treatment effects. The aflibercept-treated eyes showed a greater mean decrease in sfPEDH: ~43.9 μm (~2 times) compared to ranibizumab-treated eyes at 3 months after initial injections, however, the advantage of aflibercept was not sustainable at the one-year follow-up visit.

The slightly different effects of the two drugs on pathological CNV activity can be due to their different molecular structure and pharmacokinetics. Recent experimental study investigated the thickness and number of fenestrations of the

choriocapillaris in monkey eyes after application of both drugs and showed that aflibercept had a stronger effect compared to ranibizumab, which might result from the structure of aflibercept having a fragmented crystallizable (Fc) region [31]. The Fc-containing anti-VEGF drugs preferentially accumulate in endothelial and RPE cells which express Fc receptors and intracellular neonatal Fc receptors, which prolongs treatment effect. In addition, aflibercept has a higher affinity to VEGF-A receptor, which is a major molecule involved in increased vascular leakage and angiogenesis in wAMD, and a longer half-life than ranibizumab [32] [33]. Another possible reason is that aflibercept influences some molecules other than VEGF-A which affect vascular permeability, including VEGF-B and placental growth factors (both not inhibited by ranibizumab) [34].

This meta-analysis has some limitations that need to be taken into account. First, according to the subgroup analysis of BCVA, CRT and sfCT, the effectiveness of anti-VEGF with different baseline visual acuity might be inconsistent. Therefore, an adequate number of studies are needed for subgroup analysis based on stratification of the endpoints (except BCVA, CRT and sfCT). Second, there was a lack of enough data to evaluate the effects of enhanced choroidal thinning and resolution of intraretinal or subretinal fluid induced by aflibercept during long term follow-up. Finally, more data are needed to further compare the effect on sfPEDH between the two drugs. It also has to be emphasized that this was a meta-analysis of mostly retrospective studies and not of randomized controlled clinical trials which may have resulted in patient selection bias, etc.

In summary, this meta-analysis of observational studies compares the effectiveness between aflibercept and ranibizumab for wAMD patients in the real world. Aflibercept appeared superior in improving morphological parameters related to wAMD activity in the short term, and in slightly improving central visual function in the long term on treatment-native wAMD eyes, especially in eyes with lower baseline visual acuity.

Statement of Ethics

An ethics statement was not required for this study type, no human or animal subjects were used.

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Authors' Contributions

X.W. and C.Y. contributed to the conception of the work. J.D. and C.Y. searched the literature and extracted the data. C.Y. wrote the manuscript. X.W. revised the manuscript and produced the final version.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Tables

Table S1. PRISMA checklist.

Section/topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implication ns of key findings; systematic review registration number.	Page 2
BACKGROUND			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4
Study selection	9	State the process for selecting studies (*i.e.*, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	Page 5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 5

Continued

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Table S2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table S3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2, Figure 4, Figure 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 11 - 12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13 - 15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 16

Table S2. Characteristics of included studies.

Study	Country	Number of eyes, IVA/IVR	Study design	Follow-up (months)	Baseline BCVA, Mean (SD), IVA/IVR	Treatment regimen	Outcomes	Scores
Hata 2014 [10]	Japan	83/133	R	3	0.36 (0.39)/0.33 (0.31)	3 monthly injections (2 mg IVA/0.5mgIVR)	BCVA, CRT, sfPEDH, sfCT, Incidence of "DM"	7.5
Dirani 2015 [11]	Switzerland	47/68	R	3	Not stated	3 monthly injections (IVA/IVR)	BCVA, sfPEDH	5
Kano 2015 [12]	Japan	29/74	R	1, 3	0.292 (0.309)/0.299 (0.271)	3 monthly injections (2 mg IVA/0.5mgIVR)	BCVA, CRT, sfCT	8

Continued

Cho 2016 [13]	South Korea	38/60	R	12	0.63 (0.49)/0.66 (0.43)	3 monthly injections (2 mgIVA/0.5mgIVR) + PRN	BCVA, CRT	9
Gillies 2016 [14]	Australia	197/197	R	12	0.522 (0.606)/0.528 (0.408)	Monthly, PRN, or T&E (IVA/IVR)	BCVA	8.5
Inoue 2016 [15]	Japan	101/99	R	3, 6, 12	0.37 (0.37)/0.44 (0.33)	3 monthly injections (2 mg IVA/0.5mgIVR) + PRN	BCVA, CRT	7.5
Kim 2016/1# [16]	South Korea	21/30	R	12	0.73 (0.37)/0.86 (0.45)	3 monthly injections (2mg IVA/0.5mgIVR) + PRN	BCVA, CRT, Incidence of "DM"	9
Kim 2016/2¶ [17]	South Korea	85/155	R	3	Not stated	3 monthly injections (2 mg IVA/0.5mgIVR)	sfCT	7.5
Yun 2016 [18]	Korea	21/33	R	3	0.41 (0.29)/0.66 (0.37)	3 monthly injections (2 mg IVA/0.5mgIVR)	BCVA, sfCT	7.5
Au 2017 [19]	USA	30/35	R	1,3,6,12	0.49(0.39)/0.52(0.38)	PRN (2 mg IVA/0.5mgIVR)	BCVA, CRT, sfPEDH	8
Garweg 2017 [20]	Switzerland	106/47	R	12, 24	0.457 (0.6)/0.537 (0.566)	3 monthly injections (IVA/IVR) + T&E	BCVA, CRT	7

Table S3. Risk of bias in cohort studies using Newcastle Ottawa scale (NOS).

Studies	Selection (four scores)				Comparability (two scores)		Outcome (three scores)			Quality score
	S1	S2	S3	S4	C1	C2	O1	O2	O3	
Hata 2014 [10]	Yes	Yes	Yes	Yes	a	c,d	Yes	No	Yes	7.5
Dirani 2015 [11]	Yes	Yes	No	Yes	No	No	Yes	No	Yes	5
Kano 2015 [12]	Yes	Yes	Yes	Yes	a,b	c,d	Yes	No	Yes	8
Cho 2016 [13]	Yes	Yes	Yes	Yes	a,b	c,d	Yes	Yes	Yes	9
Gillies 2016 [14]	Yes	Yes	Yes	Yes	a,b	c	Yes	Yes	Yes	8.5
Inoue 2016 [15]	Yes	Yes	Yes	Yes	b	d	Yes	Yes	Yes	8
Kim 2016/1# [16]	Yes	Yes	Yes	Yes	a,b	c,d	Yes	Yes	Yes	9
Kim 2016/2¶ [17]	Yes	Yes	Yes	Yes	a,b	d	Yes	No	Yes	7.5
Yun 2016 [18]	Yes	Yes	Yes	Yes	a,b	d	Yes	No	Yes	7.5
Au 2017 [19]	Yes	Yes	No	Yes	a,b	c,d	Yes	Yes	Yes	8
Garweg 2017 [20]	Yes	Yes	Yes	Yes	a,b	No	Yes	Yes	Yes	7