

# 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<sup>®</sup>, Genentech Inc., South San Francisco, CA, USA) and aflibercept (EYLEA<sup>®</sup> 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  $\chi^2$  and I<sup>2</sup> 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 followup 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 ( $\chi^2$  = 19.73, df = 12, p = 0.07; I<sup>2</sup> = 39%) and at 12 months ( $\chi^2$  = 33.91, df = 13, p = 0.001; I<sup>2</sup> = 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,

(A)		Δflib	ercent		Ranil	vizumah		M	lean Difference	Mean Difference
(11)	Study or Subaroup	Mean	sn .	Total	Mean	SD To	al We	iaht IV	V Random 95% Cl	IV Bandom 95% CI
	2.4.1 Baseline logMAR	BCVA ≤	0.6	Total	Mean	00 10	ui vic	igni is	, italiaolii, 5070 Ol	
	Au 2017 [19]	-0.03	0.421	34	0	0.421	24 1	1.2%	-0.03 [-0.25, 0.19]	——————————————————————————————————————
	Garweg 2017 [20]	-0.094	0.218	106	-0.117	0.259	47 6	5.6%	0.02 [-0.06, 0.11]	+-
	Hata 2014 [10]	-0.09	0.17	83	-0.05	0.2 1	33 13	3.0%	-0.04 [-0.09, 0.01]	-
	Inoue 2016 [15]	-0.11	0.268	101	-0.1	0.292	99 7	7.5%	-0.01 [-0.09, 0.07]	+
	Kano 2015 [12]	-0.02	0.125	29	-0.085	0.164	74 10	).8%	0.07 [0.01, 0.12]	-
	Lotery 2017 [23]	-0.025	0.23	4300	-0.03	0.218 33	50 25	5.5%	0.00 [-0.01, 0.02]	<u>†</u>
	Subtotal (95% CI)			4653		37:	27 64	4.7%	0.01 [-0.02, 0.03]	•
	Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi² =	7.52, df	= 5 (P	= 0.18);	l² = 34%				
	Test for overall effect: Z	= 0.38 (P =	= 0.71)							
	2.4.2 Baseline logMAR	BCVA >0	.6							
	Gharbiya 2018 [28]	-0.098	0 166	38	-0 126	0 178	38 7	7.6%	0 03 [-0 05 0 11]	
	Kim 2016/1 [16]	-0.26	0.31	21	-0.24	0.36	30 1	1.7%	-0.02 [-0.20, 0.16]	<u> </u>
	Providencia 2018 [29]	-0.021 0	.1128	42	0.0226	0.178	30 E	3.3%	-0.04 [-0.12, 0.03]	-
	Subhi 2017 [26]	-0.11	0.314	49	-0.024	0.32	57 3	3.7%	-0.09 [-0.21, 0.03]	
	Subtotal (95% CI)			150		1	55 2 <sup>,</sup>	1.4%	-0.02 [-0.07, 0.02]	•
	Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi² =	3.02, df	= 3 (P	= 0.39);	l² = 1%				
	Test for overall effect: Z	= 0.93 (P =	= 0.35)							
	2 4 3 Other studies									
	Dirani 2015 [11]	-0 174	0 166	48	-0 124	0 202	37 G	2%	-0.05[-0.12_0.02]	
	Kava 2017 [21]	-0.174	0.100	24	0.05	0.202	28 1	1.9%	-0.00 [-0.12, 0.02]	
	Yun 2016 [18]	-0.18	0.214	21	-0.17	0.315	33 2	2.8%	-0.01 [-0.15, 0.13]	
	Subtotal (95% CI)			93		1	28 13	3.9%	-0.07 [-0.16, 0.02]	•
	Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi² =	3.32, df	= 2 (P	= 0.19);	l² = 40%				
	Test for overall effect: Z	= 1.54 (P =	= 0.12)							
	T-4-1 (05% OI)			4000		10		0.00/		
	Total (95% CI)			4896		40	0 100	0.0%	-0.01 [-0.04, 0.01]	
	Heterogeneity: $Tau^2 = 0.1$	00; Chi <sup>2</sup> =	19.73, d	f = 12	(P = 0.0)	'); l² = 39%				-1 -0.5 0 0.5 1
	Test for overall effect: Z	= 0.81 (P =	= 0.42)	df - 0	(D - 0 2)	12 - 25 0	0/			Favours [Aflibercept] Favours [Ranibizumab]
	Test for subdroub differe	nces. Chi-	- 3. IZ.	ui – z i	IP = 0.2	0.130.9	70			
(B)		Af	libercep	t	R	anibizumal	,		Mean Difference	Mean Difference
<b>(B)</b>	Study or Subgroup	Af Mean	libercep SD	t Total	R I Mear	anibizumal I SE	o Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV. Random. 95% Cl
<b>(B)</b>	Study or Subgroup 3.2.1 Baseline logMAR B	Afi <u>Mean</u> CVA≪0.6	libercep SD	t Tota	R I Mear	anibizumal <u>S</u>	Total	Weight	Mean Difference	Mean Difference
(B)	Study or Subgroup 3.2.1 Baseline logMAR B Au 2017 [19]	Afi <u>Mean</u> CVA≪0.6 0.03	0.502	t <u>Tota</u>	R <u>I Mear</u> 0.0.7	anibizumal	21	<u>Weight</u> 1.5%	Mean Difference IV. Random, 95% Cl -0.07 [-0.35, 0.21]	Mean Difference IV, Random, 95% Cl
(B)	Study or Subgroup 3.2.1 Baseline logMAR B Au 2017 [19] Garweg 2017 [20] Gillies 2016 [14]	Af <u>Mean</u> CVA≪0.6 0.03 -0.077	0.502	t Tota 30 106	R I Mear 0 0.7 6 -0.08	anibizumal <b>SE</b> 0.502 0.311 0.324	21 21 47	<b>Weight</b> 1.5% 6.9%	Mean Difference IV. Random, 95% Cl -0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12]	Mean Difference IV, Random, 95% Cl
(B)	<b>Study or Subgroup</b> <b>3.2.1 Baseline logMAR B</b> Au 2017 [19] Garweg 2017 [20] Gillies 2016 [14] Inque 2016 [15]	Afi <u>Mean</u> CVA≪0.6 0.03 -0.077 -0.096 -0.12	libercep SD 0.502 0.296 0.339 0.28	t <b>Tota</b> 30 106 146 101	R <u>Mear</u> 0 0.7 6 -0.08 6 -0.078 -0.07	anibizumal 0.502 0.311 0.324 0.32	<b>Total</b> 21 47 124 99	Weight 1.5% 6.9% 9.4% 8.9%	Mean Difference IV. Random, 95% Cl -0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.03] -0.05 [-0.13, 0.03]	Mean Difference IV. Random, 95% Cl
(B)	<b>Study or Subgroup</b> <b>3.2.1 Baseline logMAR B</b> Au 2017 [19] Garweg 2017 [20] Gillies 2016 [14] Inoue 2016 [15] Lee 2017 [22]	Afi <u>Mean</u> CVA≪0.6 0.03 -0.077 -0.096 -0.12 -0.122	libercep SD 0.502 0.296 0.339 0.28 0.313	t <u>Tota</u> 30 106 146 101 942	R Mear 0 0.7 0 -0.08 0.07 0.07 0.07 0.03	anibizumal 0.502 0.311 0.324 0.32 0.32 0.32 0.32 0.32 0.32	<b>Total</b> 21 47 124 99 942	Weight 1.5% 6.9% 9.4% 8.9% 15.8%	Mean Difference IV. Random, 95% Cl 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06]	Mean Difference IV. Random, 95% Cl
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]	Afi <u>Mean</u> CVA≤0.6 0.03 -0.077 -0.096 -0.12 -0.122 0.0038	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294	t 30 106 146 101 942 3031	R Mear 0 0.1 -0.08 -0.078 -0.078 -0.078 -0.0318 0.006	anibizumal 0.502 0.311 0.324 0.32 0.324 0.32 0.324502 0.296	21 47 124 99 942 1468	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0%	Mean Difference IV. Random, 95% Cl 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02]	Mean Difference IV. Random, 95% Cl
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)	Afi <u>Mean</u> CVA≤0.6 0.03 -0.077 -0.096 -0.12 -0.122 0.0038	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294	t Total 300 106 146 101 942 3031 4356	R Mear 0 0.1 5 -0.08 5 -0.07 6 -0.07 2 -0.031 8 0.006	anibizumal 0.502 7 0.311 3 0.324 7 0.32 3 0.344502 6 0.296	21 47 124 99 942 1468 <b>2701</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5%	Mean Difference IV. Random, 95% Cl 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01]	Mean Difference
(B) _	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00	Afi <u>Mean</u> CVA≤0.6 0.03 -0.077 -0.096 -0.12 -0.122 0.0038 0; Chi² = 25.	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df =	t Total 306 106 146 3031 4356 5 (P = 1	R Mear 0 0. -0.087 -0.078 -0.078 -0.0318 0.006 0.0001);	anibizumal 0.502 0.311 0.324 0.32 0.324 0.32 0.324 0.32 0.324 0.32 0.324 0.32 0.324 0.32 0.324 0.32 0.324 0.32 0.324 0.32 0.324 0.32 0.324 0.329 0.324 0.329	21 47 124 99 942 1468 <b>2701</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5%	Mean Difference IV. Random, 95% Cl 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01]	Mean Difference IV. Random, 95% Cl
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =	Afr <u>Mean</u> CVA≤0.6 0.03 -0.077 -0.096 -0.12 0.0038 0; Chi² = 25 1.37 (P = 0.12)	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = .17)	t <b>Tota</b> 106 146 101 942 3031 <b>4356</b> 5 (P = 1	R Mear 0 0.78 -0.078 -0.078 -0.0318 0.006 0.0001);	anibizumal 0.502 0.311 0.324 0.323 0.344502 0.296 <sup>2</sup> = 80%	21 47 124 99 942 1468 <b>2701</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% <b>59.5%</b>	Mean Difference IV. Random, 95% Cl 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.03] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B	Aff <u>Mean</u> CVA≪0.6 0.03 -0.077 -0.096 -0.122 0.0038 0; Chi <sup>2</sup> = 25 1.37 (P = 0. CVA>0.6	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = .17)	t <b>Tota</b> 106 146 101 942 3031 <b>4356</b> 5 (P = 1	R 0 0.7 0 0.087 0 0.078 0.0078 0.	anibizumal 5 SE 1 0.502 7 0.311 3 0.324 7 0.32 3 0.344502 6 0.296 2 = 80%	21 47 124 99 942 1468 <b>2701</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% <b>59.5%</b>	Mean Difference IV. Random, 95% CI 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01]	Mean Difference
(B) _	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]	Affi <u>Mean</u> CVA≤0.6 0.033 -0.077 -0.096 -0.122 -0.122 0.038 ); Chi <sup>2</sup> = 25 1.37 (P = 0 CVA>0.6 -0.19	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = .17) 0.443	t <b>Tota</b> 306 106 146 101 942 3031 <b>4356</b> 5 (P = 1	R 0 0.7 0 -0.08 0 -0.078 -	anibizumal SE 0.502 0.311 0.324 0.323 0.344502 0.344502 0.344502 0.296 2 = 80% 7 0.541	21 47 124 99 942 1468 <b>2701</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% <b>59.5%</b> 2.7%	Mean Difference IV, Random, 95% Cl 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01]	Mean Difference
(B) _	Study or Subgroup 3.2.1 Baseline logMAR B Au 2017 [19] Garweg 2017 [20] Gillies 2016 [14] Inoue 2016 [15] Lee 2017 [22] Lotery 2017 [23] Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 3.2.2 Baseline logMAR B Cho 2016 [13] Kim 2016/1 [16]	Afri Mean CVA≤0.6 0.03 -0.077 -0.096 -0.12 0.0038 0; Chi² = 25 1.37 (P = 0 CVA>0.6 -0.19 -0.15	0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.26	t <b>Tota</b> 300 106 146 101 942 3031 <b>4356</b> 5 (P = 1 38 21	R Mear 0 0.3 -0.087 -0.078 -0.078 -0.0318 0.006 0.0001); -0.17 -0.17 -0.1	anibizumal SE 0.502 0.311 0.324 0.325 0.324	21 47 124 99 942 1468 <b>2701</b> 60 30	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% <b>59.5%</b> 2.7% 3.8%	Mean Difference IV. Random. 95% Cl -0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.02 [-0.22, 0.18] -0.01 [-0.17, 0.15]	Mean Difference
(B) _	Study or Subgroup 3.2.1 Baseline logMAR B Au 2017 [19] Garweg 2017 [20] Gillies 2016 [14] Inoue 2016 [15] Lee 2017 [22] Lotery 2017 [23] Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 3.2.2 Baseline logMAR B Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24]	Affi <u>Mean</u> CVA≤0.6 0.037 -0.096 -0.12 -0.122 0.0038 0; Chi <sup>2</sup> = 25 1.37 (P = 0 CVA>0.6 -0.19 -0.15 -0.2	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = .17) 0.443 0.26 0.626	t <b>Total</b> <b>106</b> 146 101 942 3031 <b>4356</b> <b>5</b> (P = 1) <b>38</b> <b>21</b> 74	R Mear 0 0.3 -0.083 -0.078 -0.078 -0.0318 0.006 0.0001); -0.14 -0.18 -0.18	anibizumal SE 0.502 0.311 0.324	21 47 124 99 942 1468 <b>2701</b> 60 30 87	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5%	Mean Difference IV. Random. 95% Cl -0.07 [-0.35, 0.21] 0.01 [-0.10, 0.02] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.02 [-0.22, 0.18] -0.01 [-0.17, 0.15] -0.01 [-0.22, 0.20]	Mean Difference
(B) _	Study or Subgroup 3.2.1 Baseline logMAR B Au 2017 [19] Garweg 2017 [20] Gillies 2016 [14] Inoue 2016 [15] Lee 2017 [22] Lotery 2017 [23] Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 3.2.2 Baseline logMAR B Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Raemusean 2017 [25]	Affi <u>Mean</u> CVA≤0.6 0.037 -0.096 -0.12 0.0038 0; Chi <sup>2</sup> = 25 1.37 (P = 0 CVA>0.6 -0.19 -0.15 -0.2 -0.0548 -0.19	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = .17) 0.443 0.26 0.626 0.626 0.626	t <b>Total</b> <b>Total</b> <b>106</b> <b>146</b> <b>101</b> <b>942</b> <b>3031</b> <b>4356</b> <b>5</b> (P = 1) <b>38</b> <b>21</b> <b>74</b> <b>42</b> <b>5</b>	R Mear 0 0.7 -0.08 -0.078 -0.0318 0.000 0.0001); -0.18 -0.18 -0.0614	anibizumal SE 0.502 0.311 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.344502 0.344502 0.324 0.322 0.324 0.322 0.324 0.344	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.4%	Mean Difference IV. Random, 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.01 [-0.17, 0.15] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.08, 0.10]	Mean Difference
(B) _	Study or Subgroup 3.2.1 Baseline logMAR B Au 2017 [19] Garweg 2017 [20] Gillies 2016 [14] Inoue 2016 [15] Lee 2017 [22] Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 3.2.2 Baseline logMAR B Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Rasmussen 2017 [25] Subhi 2017 [26]	Aff <u>Mean</u> CVA≤0.6 0.037 -0.096 -0.12 0.0038 0; Chi <sup>2</sup> = 25 1.37 (P = 0. CVA>0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.26 0.626 0.1412 0.766 0.346	t <b>Total</b> <b>Total</b> <b>106</b> <b>106</b> <b>106</b> <b>101</b> <b>942</b> <b>3031</b> <b>4356</b> <b>5</b> (P = 1) <b>38</b> <b>4356</b> <b>5</b> (P = 1) <b>4356</b> <b>5</b> (P = 1) <b>4356</b> <b>5</b> (P = 1) <b>5</b> (P = 1) <b>5</b> (P = 1) <b>5</b> (P	R Mear 0 0.7 -0.078 -0.078 -0.078 -0.078 -0.078 -0.078 -0.078 -0.18 -0.18 -0.128 -0.0614 -0.128 0 0.0	anibizumal SE 0.502 0.311 0.324 0.344	<b>Total</b> 21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 57	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.4% 5.3%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.02 [-0.22, 0.18] -0.01 [-0.17, 0.15] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.04]	Mean Difference
(B) _	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% Cl)	Affi <u>Mean</u> CVA≤0.6 0.037 -0.096 -0.12 0.0038 0; Chi <sup>2</sup> = 25 1.37 (P = 0 CVA>0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.078	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.26 0.626 0.1412 0.706 0.346	t Total 300 106 1466 101 9422 3031 4356 55 (P = 1 38 21 74 22 52 74 99 751	R Mear 0 0.7 -0.078 -0.078 -0.078 -0.078 -0.0318 0.0001); -0.18 0.00614 -0.128 0.00614 -0.128 0.00614	anibizumal SE 0.502 0.311 0.324 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.344502 0.324 0.321 0.324 0.3221 0.3221 0.3221 0.324 0.344 0.324 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344	<b>Total</b> 21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 57 <b>880</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.4% 5.3% 31.0%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.01 [-0.22, 0.18] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.09 [-0.22, 0.04]	Mean Difference
(B) _	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00	Aff Mean $CVA \leq 0.6$ 0.037 -0.096 -0.12 0.0038 0; Chi2 = 25 1.37 (P = 0. CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548 -0.121 -0.078 0; Chi2 = 4.4	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.26 0.626 0.626 0.1412 0.706 0.346 5, df = 5	t Total 300 146 101 942 3031 4356 55 (P = 1 388 211 74 4356 57 74 751 (P = 0	R Mear 0 0.7 -0.078 -0.078 -0.078 -0.0318 0.0001); -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.00128 0.00128 0.00128 -0.0128 0.00128 -0.0128 0.00128 -0.0128 -0.0128 -0.0128 -0.0128 -0.018	anibizumal <u>SE</u> 0.502 0.311 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.324 0.321 0.824 0.327 0%	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 57 <b>880</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.3% 8.4% 5.3% 31.0%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.02 [-0.22, 0.18] -0.01 [-0.17, 0.15] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.08, 0.10] -0.09 [-0.22, 0.04] -0.05 [-0.10, -0.00]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =	Affi Mean $CVA \leq 0.6$ 0.037 -0.096 -0.12 0.0038 0.077 -0.096 -0.122 0.0038 0.078 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.26 0.626 0.626 0.1412 0.706 0.346 5, df = 5 .05)	t Total 300 1466 101 9422 3031 4356 55 (P = 1 388 211 74 4356 74 425 57 49 751 (P = 0	R Mear 0 0.7 -0.08 -0.078 -0.078 -0.0318 0.0000 0.00001); -0.18 -0.18 0.0614 -0.128 0.0614 -0.128 0.00128 0.00128 0.00128 -0.0128 0.00128 -0.0128 0.00128 -0.0128 0.00128 -0.0128 -0.018 -0.	anibizumal SE 0.502 0.311 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.344502 0.324 0.327 0.724 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.329 0.824 0.329 0.824 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.324 0.8	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 57 <b>880</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.3% 8.4% 5.3% 31.0%	Mean Difference IV. Random, 95% Cl 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.02 [-0.22, 0.18] -0.01 [-0.17, 0.15] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.04] -0.05 [-0.10, -0.00]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies	Affi Mean $CVA \le 0.6$ 0.03 -0.07 -0.12 -0.122 0.0038 $0; Chi^2 = 25$ 1.37 (P = 0 CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.078 -0.121 -0.0548 -0.121 -0.078 -0.121 -0.0548 -0.121 -0.078 -0.121 -0.0548 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.121 -0.078 -0.190 -0.121 -0.078 -0.190 -0.121 -0.078 -0.190 -0.19	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.26 0.626 0.1412 0.706 0.346 0.346 5, df = 5 05)	t Total 300 1060 1466 1011 9422 3031 4356 55 (P = 1) 388 211 74 435 57 49 751 (P = 0.	R Mear 0 0.7 -0.08 -0.078 -0.0318 0.000 0.0001); -0.18 0.00614 -0.18 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128	anibizumal SE 0.502 0.311 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.344502 0.344502 0.3247 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.327 0.824 0.329 0.824 0.324 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.329 0.844 0.324 0.824	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 57 <b>880</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.3% 8.3% 31.0%	Mean Difference IV. Random, 95% Cl 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.02 [-0.22, 0.18] -0.01 [-0.17, 0.15] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.04] -0.05 [-0.10, -0.00]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies           De Massougnes 2018 [27]	Aff Mean $CVA \le 0.6$ 0.03 -0.07 -0.096 -0.12 0.0038 0; Chi2 = 25 1.37 (P = 0. CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548 -0.121 -0.078 0; Chi2 = 4.4 1.96 (P = 0 -0.136	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.26 0.626 0.1412 0.706 0.346 5, df = 5 05) 0.258	t Total 300 146 101 942 3031 4356 55 (P = 1 388 211 74 4356 751 749 751 (P = 0 411 (P = 0)	R Mear 0 0.7 -0.078 -0.078 -0.078 -0.078 -0.078 -0.078 -0.128 0.001 -0.128 0.001 -0.128 -0.18 -0.018 -0.1	anibizumal SE 0.502 0.311 0.324 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.327 0.5441 0.327 0.5441 0.327 0.5441 0.327 0%	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 57 <b>880</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.3% 31.0% 7.1%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.02 [-0.22, 0.18] -0.01 [-0.17, 0.15] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.08, 0.10] -0.09 [-0.22, 0.04] -0.05 [-0.10, -0.00]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies           De Massougnes 2018 [27]           Smit 2018 [30]	Aff Mean $CVA \le 0.6$ 0.03 -0.07 -0.096 -0.12 0.0038 $0; Chi^2 = 25$ 1.37 (P = 0. CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548 -0.121 -0.078 $0; Chi^2 = 4.4$ 1.96 (P = 0 -0.136 0.012	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.266 0.626 0.1412 0.706 0.346 15, df = 5 05) 0.258 0.34	t Total 3001 1466 1011 9422 30031 4356 55 (P = 1) 388 211 744 4356 55 (P = 1) 749 751 (P = 0) 411 37	R Mear 0 0.7 -0.078 -0.078 -0.078 -0.078 -0.078 -0.078 -0.18 0.0001); -0.128 0.001 -0.128 -0.18 -0.	anibizumal SE 0.502 0.311 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.324 0.327 0% 2.0.266 7.0.541 0.327 0%	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 57 <b>880</b> 63 30	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.3% 31.0% 7.1% 2.4%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] 0.01 [-0.22, 0.20] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.05 [-0.10, -0.00]	Mean Difference IV. Random. 95% Cl
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies           De Massougnes 2018 [27]           Smit 2018 [30]           Subtotal (95% CI)	Aff Mean $CVA \le 0.6$ 0.037 -0.096 -0.12 0.0038 $0; Chi^2 = 25$ 1.37 (P = 0.0000000000000000000000000000000000	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.266 0.626 0.1412 0.706 0.346 5, df = 5 0.5) 0.258 0.34	t Total 300 146 101 942 3031 4356 5 (P = 1 388 21 74 4356 (P = 0 (P = 0 41 37 78 (P	R Mear 0 0.7 -0.078 -0.078 -0.078 -0.0318 0.0001); -0.182 0.00128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.018 -0	anibizumal SE 0.502 0.311 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.54 0.327 0.54 0.327 0.54 0.327 0.54 0.327 0.54 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.545 0.296 0.327 0.545 0.327 0.545 0.327 0.327 0.545 0.327 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.327 0.545 0.545 0.327 0.545 0.557 0.57	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 65 57 <b>880</b> 63 30 <b>93</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.3% 31.0% 7.1% 2.4% 9.5%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] 0.01 [-0.22, 0.20] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.20] -0.09 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.05 [-0.10, -0.00] 0.05 [-0.06, 0.15] -0.16 [-0.37, 0.05] -0.03 [-0.23, 0.16]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies           De Massougnes 2018 [27]           Smit 2018 [30]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.01           Test for overall effect: 2 =	Aff <u>Mean</u> CVA ≤0.6 0.03 -0.07 -0.096 -0.12 0.0038 0; Chi <sup>2</sup> = 25 1.37 (P = 0. CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548 -0.121 -0.078 0; Chi <sup>2</sup> = 4.4 1.96 (P = 0 -0.136 0.012 1; Chi <sup>2</sup> = 2.8 0 34 (P = 0	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.266 0.626 0.1412 0.706 0.346 15, df = 5 0.5) 0.258 0.34 0.34 0.6, df = 1 73)	t Total 3001 4356 5 (P = 1) 388 211 744 4356 5 (P = 1) 388 211 744 4356 (P = 0) 411 3778 78 (P = 0)	R Mear 0 0.7 -0.078 -0.078 -0.078 -0.078 -0.0318 0.0001); -0.182 0.001 -0.128 0.001 -0.128 0.001 -0.128 -0.182	anibizumal SE 0.502 0.311 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.545 0.266 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.52 0.52 0.55	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 67 <b>880</b> 63 30 <b>93</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.4% 5.3% 31.0% 7.1% 2.4% 9.5%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] 0.01 [-0.22, 0.20] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.20] -0.09 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.05 [-0.10, -0.00] 0.05 [-0.06, 0.15] -0.16 [-0.37, 0.05] -0.03 [-0.23, 0.16]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies           De Massougnes 2018 [27]           Smit 2018 [30]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.01           Test for overall effect: Z = 1	Aff Mean $CVA \le 0.6$ 0.03 -0.07 -0.096 -0.12 0.0038 $0; Chi^2 = 25$ 1.37 (P = 0. CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548 -0.122 -0.0548 -0.122 -0.0548 -0.122 -0.0548 -0.126 -0.0122 -0.0126 -0.012	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.266 0.626 0.1412 0.706 0.346 15, df = 5 0.5) 0.258 0.34 6, df = 1 73)	t Total 3001 1466 1011 9422 30031 4356 5 (P = 1) 388 211 744 4356 5 (P = 0) 413 778 78 (P = 0)	R Mear 0 0. -0.078 -0.078 -0.078 -0.0318 0.0001); -0.142 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.128 0.0014 -0.015 -0.018 -0.015 -0.018 -0.0018 -0.	anibizumal SE 0.502 0.311 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.344502 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0% 2.0.266 7.0.51 65%	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 57 <b>880</b> 63 30 <b>93</b>	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.4% 5.3% 31.0% 7.1% 2.4% 9.5%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] 0.01 [-0.22, 0.20] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.05 [-0.10, -0.00] 0.05 [-0.06, 0.15] -0.16 [-0.37, 0.05] -0.03 [-0.23, 0.16]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies           De Massougnes 2018 [27]           Smit 2018 [30]           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.01           Test for overall effect: Z = 1           Total (95% Cl)	Aff Mean $CVA \le 0.6$ 0.037 -0.096 -0.12 0.0038 $0; Chi^2 = 25$ 1.37 (P = 0. CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.0548 -0.122 -0.0548 -0.122 -0.0548 -0.0122 -0.0126 -0.0126 -0.0126 -0.0126 -0.0126 -0.034 (P = 0)	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 177) 0.443 0.26 0.626 0.1412 0.706 0.346 0.5, df = 5 0.5) 0.258 0.34 86, df = 1 73)	t Total 3001 1466 1011 9422 30031 4356 5 (P = 1) 388 211 4356 5 (P = 1) 4356 4356 749 751 (P = 0) 411 378 78 (P = 0) 5185	R Mear 0 0.7 -0.078 -0.078 -0.0318 0.0000 0.00001); -0.128 0.0614 -0.128 0.0614 -0.128 0.0614 -0.128 0.001 -0.185 0.001 -0.185 -0.1	anibizumal SE 0.502 0.311 0.324 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.327 0.544 0.327 0.724 0.327 0% 2.0.266 7.0.51 65%	211 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 65 7 <b>880</b> 63 30 <b>93</b> 3674	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.4% 5.3% 31.0% 7.1% 2.4% 9.5%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] 0.01 [-0.22, 0.20] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.20] -0.09 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.05 [-0.10, -0.00] 0.05 [-0.06, 0.15] -0.16 [-0.37, 0.05] -0.03 [-0.23, 0.16] -0.04 [-0.07, -0.00]	Mean Difference
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies           De Massougnes 2018 [27]           Smit 2018 [30]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.01           Test for overall effect: Z = 1           Total (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00	Aff Mean CVA ≤ 0.6 0.03 -0.077 -0.096 -0.12 -0.122 0.038 0; Chi <sup>2</sup> = 25 1.37 (P = 0 CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.078 0.0121 -0.078 0.0121 -0.0548 -0.121 -0.078 0.0121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.0548 -0.121 -0.058 -0.012 -0.054 -0.012 -0.058 -0.012 -0.058 -0.012 -0.058 -0.012 -0.058 -0.012 -0.058 -0.012 -0.058 -0.012 -0.058 -0.012 -0.058 -0.058 -0.012 -0.058	libercep SD 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.266 0.626 0.1412 0.706 0.346 15, df = 5 0.5) 0.258 0.34 6, df = 1 73) 91, df =	t Total 3001 44356 5 (P = 1) 3031 4356 5 (P = 1) 388 211 4356 5 (P = 1) 4356 4356 (P = 0) 411 37 78 (P = 0) 51855 13 (P = 1) 5 (P = 1	R Mear 0 0.7 -0.07 -0.12 -0.07 -0.12 -0.07 -0.12 -0.07 -0.07 -0.07 -0.07 -0.07 -0.12 -0.07 -0.12 -0.18 -0.17 -0.12 -0.17 -0.18 -0.17 -0.18 -0.17 -0.18 -0.17 -0.18 -0.17 -0.18 -0.17 -0.18 -0.17 -0.18 -0.17 -0.18 -0.17 -0.18 -0.17 -0.18 -0.07 -0.18 -0.07 -0.18 -0.07 -0.18 -0.07 -0.18 -0.07 -0.18 -0.07 -0.18 -0.07 -0.18 -0.07 -0.07 -0.18 -0.07	anibizumal SE 0.502 0.312 0.324 0.324 0.324 0.324 0.324 0.324 0.324 0.296 2 = 80% 0.544 0.327 0.724 0.2212 3 0.824 0.327 0% 2 0.266 7 0.51 35% 2 = 62%	211 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 657 <b>880</b> 63 30 <b>93</b> 3674	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.4% 5.3% 31.0% 7.1% 2.4% 9.5%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.01 [-0.22, 0.20] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.20] -0.09 [-0.22, 0.04] -0.09 [-0.22, 0.04] -0.05 [-0.10, -0.00] 0.05 [-0.06, 0.15] -0.16 [-0.37, 0.05] -0.03 [-0.23, 0.16] -0.04 [-0.07, -0.00]	Mean Difference IV. Random. 95% Cl
(B)	Study or Subgroup           3.2.1 Baseline logMAR B           Au 2017 [19]           Garweg 2017 [20]           Gillies 2016 [14]           Inoue 2016 [15]           Lee 2017 [22]           Lotery 2017 [23]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.2 Baseline logMAR B           Cho 2016 [13]           Kim 2016/1 [16]           Park 2017 [24]           Providencia 2018 [29]           Rasmussen 2017 [25]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z =           3.2.3 Other studies           De Massougnes 2018 [27]           Smit 2018 [30]           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.01           Test for overall effect: Z = 1           Total (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.02           Test for overall effect: Z = 1           Total (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.02           Test for overall effect: Z = 1	Afi Mean CVA ≤0.6 0.03 -0.077 -0.096 -0.12 -0.122 0.0038 ); Chi <sup>2</sup> = 25 1.37 (P = 0 CVA > 0.6 -0.19 -0.15 -0.2 -0.0548 -0.121 -0.078 -0.121 -0.078 ); Chi <sup>2</sup> = 4.4 1.96 (P = 0 -0.136 0.012 i; Chi <sup>2</sup> = 2.8 0.34 (P = 0 ); Chi <sup>2</sup> = 33 2.03 (P = 2	libercep 0.502 0.296 0.339 0.28 0.313 0.294 24, df = 17) 0.443 0.266 0.626 0.1412 0.706 0.346 15, df = 5 0.5) 0.258 0.34 6, df = 1 73) 91, df = 0.418 df =	t Total 3001 4356 5 (P = 1) 3031 5 (P = 0) 413 751 (P = 0) 5185 13 (P = 2 (P = 2) 5 (P = 2) 5 (P = 1) 5 (P = 1) 5 (P = 2) 5 (P	R Mear 0 0.7 -0.078 -0.078 -0.078 -0.0318 0.0001); -0.182 0.00128 -0.182 0.0014 -0.128 0.0014 -0.128 0.001 -0.182 -0.182 -0.182 -0.182 -0.182 -0.182 -0.015 -0.128 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.128 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.001 -0.128 -0.015 -0.015 -0.015 -0.015 -0.001 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.015 -0.001 -0.015 -0.001 -0.001 -0.015 -0.001 -0.015 -0.001 -0.015 -0.001 -0.015 -0.001 -0.	anibizumal SE 0.502 0.311 0.324 0.324 0.324 0.326 0.344502 0.344502 0.344502 0.344502 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.545 0.266 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.52 0.51 0.524 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.544 0.327 0.545 0.545 0.524 0.327 0.545 0.545 0.524 0.327 0.545 0.545 0.524 0.327 0.545 0.555 0.5577 0.557 0.557 0.557 0.557 0.557 0.557	21 47 124 99 942 1468 <b>2701</b> 60 30 87 30 616 67 <b>880</b> 63 30 <b>93</b> 3674	Weight 1.5% 6.9% 9.4% 8.9% 15.8% 17.0% 59.5% 2.7% 3.8% 2.5% 8.3% 8.4% 5.3% 31.0% 7.1% 2.4% 9.5%	Mean Difference IV. Random. 95% CI 0.07 [-0.35, 0.21] 0.01 [-0.10, 0.12] -0.02 [-0.10, 0.06] -0.05 [-0.13, 0.03] -0.09 [-0.12, -0.06] -0.00 [-0.02, 0.02] -0.04 [-0.09, 0.01] -0.01 [-0.17, 0.15] -0.01 [-0.22, 0.20] -0.12 [-0.21, -0.03] 0.01 [-0.22, 0.20] -0.05 [-0.10, -0.00] 0.05 [-0.06, 0.15] -0.06 [-0.37, 0.05] -0.03 [-0.23, 0.16] -0.04 [-0.07, -0.00]	Mean Difference IV. Random. 95% Cl

**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 ( $\chi^2 = 8.39$ , df = 8, p = 0.4; I<sup>2</sup> = 5%) and 12 months ( $\chi^2 = 4.40$ , df = 7, p = 0.73; I<sup>2</sup> = 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 ( $\chi^2 = 30.68$ , df = 5, p < 0.0001; I<sup>2</sup> = 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

(A)		Af	libercept		Ran	ibizumat			Mean Difference	Mean Difference
` '	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	5.1.1 Baseline logMAF	R BCVA ≤	0.6					-		
	Au 2017 [19]	-44.13	86.69	34	-52.18	86.69	24	14.4%	8.05 [-37.25, 53.35]	+
	Garweg 2017 [20]	-131.24	156.43	106	-136.65	163.15	47	9.6%	5.41 [-49.93, 60.75]	+
	Hata 2014 [10]	-142.2	136.2	83	-146.4	169.3	133	17.5%	4.20 [-36.87, 45.27]	+
	Inoue 2016 [15]	-97	123.077	101	-122	129.3	99	24.1%	25.00 [-10.00, 60.00]	+ <b>=</b> -
	Kano 2015 [12]	-78	125	29	-52	115	74	10.7%	-26.00 [-78.50, 26.50]	
	Subtotal (95% CI)			353			377	76.3%	7.41 [-12.26, 27.07]	◆
	Heterogeneity: Chi <sup>2</sup> = 2	.56, df = 4	(P = 0.63)	; l <sup>2</sup> = 0	%					
	Test for overall effect: Z	. = 0.74 (P	= 0.46)	,						
	5 1 2 Baseline logMAE		. 0.6							
	Charbing 2019 [29]	107 0	110 5	20	00 6	110 E	20	11 40/	49 70 [ 00 51 0 11]	
	Gharbiya 2016 [20]	-137.3	166 54	30	-00.0	244 72	30	11.4%	-46.70 [-99.51, 2.11]	
	Nifi 2010/1 [10]	-139.9	100.04	21	- 101.5	241.73	30	2.3%	21.00 [-90.45, 133.05]	
		-119.4	122 142	42	-20.2	192.24	50	0.3%	-91.20 [-430.54, 246.14]	
	Subni 2017 [26]	-148	132.143	49	-114	157.93	5/ 155	9.7%		
		00 -16 - 0	(D - 0.74)	150	<b>n</b> /		155	23.1%	-30.19 [-/ 1.4/, -0.92]	•
	Heterogeneity: Chi <sup>2</sup> = 1	.36, at = 3	(P = 0.71)	$1^{*} = 0^{*}$	%					
	l est for overall effect: 2	. = 2.01 (P	= 0.04)							
	Total (95% CI)			503			532	100.0%	-2.93 [-20.10, 14.25]	•
	Heterogeneity: Chi <sup>2</sup> = 8	.39. df = 8	(P = 0.40)	: l <sup>2</sup> = 5	%				• / •	
	Test for overall effect: Z	= 0.33 (P	= 0.74)							-500 -250 0 250 500
	Test for subaroup differ	ences: Ch	i² = 4.48. c	if = 1 (F	P = 0.03).	l² = 77.79	%			Favours [Aflibercept] Favours [Ranibizumab]
(R)		Δf	ibercent		Ran	ihizumah	,		Mean Difference	Mean Difference
(D)	Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed, 95% CI	IV. Fixed, 95% Cl
-	Class C. Canglerap									
	6.1.1 Baseline logMAR	BCVA ≤	0.6							
	6.1.1 Baseline logMAR	BCVA ≤	<b>0.6</b> 91.63	30	-63 66	91.63	21	17 2%	20 56 [-30 54 71 66]	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20]	BCVA ≤ -43.1 -125.68	91.63	30 106	-63.66 -140 21	91.63 127 89	21 47	17.2% 20.9%	20.56 [-30.54, 71.66] 14 53 [-31 80  60 86]	
	6.1.1 Baseline logMAF Au 2017 [19] Garweg 2017 [20] Inque 2016 [15]	BCVA ≤ -43.1 -125.68 -95	91.63 149.44 113	30 106 101	-63.66 -140.21 -103	91.63 127.89 130	21 47 99	17.2% 20.9% 39.3%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8 00 [-25 78 41 78]	
	6.1.1 Baseline logMAF Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI)	<b>BCVA</b> ≤ -43.1 -125.68 -95	<b>0.6</b> 91.63 149.44 113	30 106 101 <b>237</b>	-63.66 -140.21 -103	91.63 127.89 130	21 47 99 <b>167</b>	17.2% 20.9% 39.3% <b>77.5%</b>	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63</b> ]	+ +- *
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0.	<b>BCVA</b> ≪ -43.1 -125.68 -95	91.63 91.63 149.44 113 (P = 0.92)	30 106 101 <b>237</b> :   <sup>2</sup> = 09	-63.66 -140.21 -103 %	91.63 127.89 130	21 47 99 <b>167</b>	17.2% 20.9% 39.3% <b>77.5%</b>	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b>	+ +- ●
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% Cl) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z	<b>BCVA</b> ≪ -43.1 -125.68 -95 17, df = 2 = 1.02 (P	91.63 149.44 113 (P = 0.92) = 0.31)	30 106 101 <b>237</b> ;   <sup>2</sup> = 09	-63.66 -140.21 -103 %	91.63 127.89 130	21 47 99 <b>167</b>	17.2% 20.9% 39.3% <b>77.5%</b>	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b>	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z	BCVA ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P	91.63 91.63 149.44 113 (P = 0.92) = 0.31)	30 106 101 <b>237</b> ;   <sup>2</sup> = 09	-63.66 -140.21 -103 %	91.63 127.89 130	21 47 99 <b>167</b>	17.2% 20.9% 39.3% <b>77.5%</b>	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b>	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z	<b>BCVA</b> ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P <b>BCVA</b> >	91.63 91.63 149.44 113 (P = 0.92) = 0.31) <b>0.6</b> 317.39	30 106 101 <b>237</b> ;   <sup>2</sup> = 09	-63.66 -140.21 -103 %	91.63 127.89 130	21 47 99 <b>167</b>	17.2% 20.9% 39.3% <b>77.5%</b>	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b>	•
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016 (115)	<b>BCVA</b> ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P <b>BCVA</b> > -184 -122 9	<b>0.6</b> 91.63 149.44 113 (P = 0.92) = 0.31) <b>0.6</b> 317.39	30 106 101 <b>237</b> ;   <sup>2</sup> = 09	-63.66 -140.21 -103 % -162 -139.6	91.63 127.89 130 362.34	21 47 99 <b>167</b> 60	17.2% 20.9% 39.3% <b>77.5%</b> 2.4%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b>	• • •
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24]	ECVA ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P ECVA > -184 -122.9 -217.88	<b>0.6</b> 91.63 149.44 113 (P = 0.92) = 0.31) <b>0.6</b> 317.39 146.304 567.405	30 106 101 <b>237</b> ;   <sup>2</sup> = 09 38 21 74	-63.66 -140.21 -103 % -162 -139.6 -171.87	91.63 127.89 130 362.34 208.947 485.31	21 47 99 <b>167</b> 60 30	17.2% 20.9% 39.3% <b>77.5%</b> 2.4% 4.7%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] 46 01 [-21.067, 118,65]	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Pervidencia 2018 [29]	<b>BCVA</b> ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P <b>BCVA</b> > -184 -122.9 -217.88	<b>0.6</b> 91.63 149.44 113 (P = 0.92) = 0.31) <b>0.6</b> 317.39 146.304 567.405	30 106 101 <b>237</b> ;   <sup>2</sup> = 09 38 21 74	-63.66 -140.21 -103 % -162 -139.6 -171.87 51.52	91.63 127.89 130 362.34 208.947 485.31	21 47 99 <b>167</b> 60 30 87	17.2% 20.9% 39.3% <b>77.5%</b> 2.4% 4.7% 1.7%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] -46.01 [-210.67, 118.65] 0.48 (40 7.9, 318.83]	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Subbi 2017 [26]	BCVA ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P BCVA > -184 -184 -122.9 -217.88 -142 -142	<b>0.6</b> 91.63 149.44 113 (P = 0.92) = 0.31) <b>0.6</b> 317.39 146.304 567.405 845.58	30 106 101 <b>237</b> ;   <sup>2</sup> = 09 38 21 74 42	-63.66 -140.21 -103 % -162 -139.6 -171.87 -51.52	91.63 127.89 130 362.34 208.947 485.31 893.13	21 47 99 <b>167</b> 60 30 87 30	17.2% 20.9% 39.3% 77.5% 2.4% 4.7% 1.7% 0.3%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] -46.01 [-210.67, 118.65] -90.48 [-499.79, 318.83] 47.00 [144.72, 10.72]	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Subhotal (95% CI)	RBCVA ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P RBCVA > -184 -122.9 -217.88 -142 -142	0.6 91.63 149.44 113 (P = 0.92) = 0.31) 0.6 317.39 146.304 567.405 845.58 137.5	30 106 101 <b>237</b> ;   <sup>2</sup> = 09 38 21 74 42 49 <b>224</b>	-63.66 -140.21 -103 % -162 -139.6 -171.87 -51.52 -95	91.63 127.89 130 362.34 208.947 485.31 893.13 165.634	21 47 99 <b>167</b> 60 30 87 30 57 <b>264</b>	17.2% 20.9% 39.3% 77.5% 2.4% 4.7% 1.7% 0.3% 13.5% 22.5%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] -46.01 [-210.67, 118.65] -90.48 [-499.79, 318.83] -47.00 [-104.72, 10.72] -31.42 [-76.05 13.21]	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 1	<b>RBCVA</b> ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P <b>RBCVA</b> > -184 -122.9 -217.88 -142 -142	0.6 91.63 149.44 113 (P = 0.92) = 0.31) 0.6 317.39 146.304 567.405 845.58 137.5	30 106 101 <b>237</b> ;   <sup>2</sup> = 09 38 21 74 42 49 <b>224</b>	-63.66 -140.21 -103 % -162 -139.6 -171.87 -51.52 -95	91.63 127.89 130 362.34 208.947 485.31 893.13 165.634	21 47 99 <b>167</b> 60 30 87 30 57 <b>264</b>	17.2% 20.9% 39.3% 77.5% 2.4% 4.7% 1.7% 0.3% 13.5% <b>22.5%</b>	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] -46.01 [-210.67, 118.65] -90.48 [-499.79, 318.83] -47.00 [-104.72, 10.72] - <b>31.42 [-76.05, 13.21]</b>	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Subhi 2017 [26] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 1. Test for overall effect: Z	R BCVA ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P R BCVA ≥ -184 -122.9 -217.88 -142 -142 -142 -142 -142 -142 -142 -142	0.6 91.63 149.44 113 (P = 0.92) = 0.31) 0.6 317.39 146.304 567.405 845.58 137.5 (P = 0.85) = 0.17)	30 106 101 <b>237</b> ;   <sup>2</sup> = 09 38 21 74 42 49 <b>224</b> ;   <sup>2</sup> = 09	-63.66 -140.21 -103 % -162 -139.6 -171.87 -51.52 -95 %	91.63 127.89 130 362.34 208.947 485.31 893.13 165.634	21 47 99 <b>167</b> 60 30 87 30 57 <b>264</b>	17.2% 20.9% 39.3% 77.5% 2.4% 4.7% 1.7% 0.3% 13.5% 22.5%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] -46.01 [-210.67, 118.65] -90.48 [-499.79, 318.83] -47.00 [-104.72, 10.72] - <b>31.42 [-76.05, 13.21]</b>	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Subhi 2017 [26] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 1. Test for overall effect: Z	R BCVA ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P R BCVA > -184 -122.9 -217.88 -142 -142 -142 -142 -34, df = 4 = 1.38 (P	0.6 91.63 149.44 113 (P = 0.92) = 0.31) 0.6 317.39 146.304 567.405 845.58 137.5 (P = 0.85) = 0.17)	30 106 101 <b>237</b> ;   <sup>2</sup> = 0? 38 21 74 42 49 <b>224</b> ;   <sup>2</sup> = 0?	-63.66 -140.21 -103 % -162 -139.6 -171.87 -51.52 -95 %	91.63 127.89 130 362.34 208.947 485.31 893.13 165.634	21 47 99 <b>167</b> 60 30 87 30 57 <b>264</b>	17.2% 20.9% 39.3% 77.5% 2.4% 4.7% 1.7% 0.3% 13.5% 22.5%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] -46.01 [-210.67, 118.65] -90.48 [-499.79, 318.83] -47.00 [-104.72, 10.72] - <b>31.42 [-76.05, 13.21]</b>	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 1. Total (95% CI)	R BCVA ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P R BCVA ≥ -184 -122.9 -217.88 -142 -142 -142 -142 -142 -142 -142 -142	<b>0.6</b> 91.63 149.44 113 (P = 0.92) = 0.31) <b>0.6</b> 317.39 146.304 567.405 845.58 137.5 (P = 0.85) = 0.17)	$30 \\ 106 \\ 101 \\ 237 \\ ;  ^2 = 0? \\ 38 \\ 21 \\ 74 \\ 42 \\ 49 \\ 224 \\ ;  ^2 = 0? \\ 461 \\ 12 = 0? \\ 461 \\ 12 = 0? \\ 461 \\ 42 \\ 43 \\ 44 \\ 44 \\ 44 \\ 44 \\ 44 \\ 44 \\ 44$	-63.66 -140.21 -103 % -162 -139.6 -171.87 -51.52 -95 %	91.63 127.89 130 362.34 208.947 485.31 893.13 165.634	21 47 99 <b>167</b> 60 30 87 30 57 <b>264</b> <b>431</b>	17.2% 20.9% 39.3% 77.5% 2.4% 4.7% 1.7% 0.3% 13.5% 22.5%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] -46.01 [-210.67, 118.65] -90.48 [-499.79, 318.83] -47.00 [-104.72, 10.72] - <b>31.42 [-76.05, 13.21]</b>	
	6.1.1 Baseline logMAR Au 2017 [19] Garweg 2017 [20] Inoue 2016 [15] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z 6.1.2 Baseline logMAR Cho 2016 [13] Kim 2016/1 [16] Park 2017 [24] Providencia 2018 [29] Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 1. Test for overall effect: Z Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4.	<b>R BCVA</b> ≤ -43.1 -125.68 -95 17, df = 2 = 1.02 (P <b>R BCVA</b> > -184 -122.9 -217.88 -142 -142 -142 -34, df = 4 = 1.38 (P	<b>0.6</b> 91.63 149.44 113 (P = 0.92) = 0.31) <b>0.6</b> 317.39 146.304 567.405 845.58 137.5 (P = 0.85) = 0.17) (P = 0.73)	$30 \\ 106 \\ 101 \\ 237 \\ ;  ^2 = 0? \\ 38 \\ 21 \\ 74 \\ 42 \\ 49 \\ 224 \\ ;  ^2 = 0? \\ 461 \\ ;  ^2 = 0? \\ 461$	-63.66 -140.21 -103 % -162 -139.6 -171.87 -51.52 -95 %	91.63 127.89 130 362.34 208.947 485.31 893.13 165.634	21 47 99 <b>167</b> 60 30 87 30 57 <b>264</b> <b>431</b>	17.2% 20.9% 39.3% 77.5% 4.7% 1.7% 0.3% 13.5% 22.5%	20.56 [-30.54, 71.66] 14.53 [-31.80, 60.86] 8.00 [-25.78, 41.78] <b>12.55 [-11.52, 36.63]</b> -22.00 [-158.34, 114.34] 16.70 [-80.80, 114.20] -46.01 [-210.67, 118.65] -90.48 [-499.79, 318.83] -47.00 [-104.72, 10.72] -31.42 [-76.05, 13.21] 2.64 [-18.55, 23.83]	

**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;

		Aflibercept		I	Ranibizumab			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% 0	CI IV. Random, 95% CI
11.2.1 Baseline logM	AR BCV	∕A ≪0.6							
Hata 2014 [10]	-25.1	25.6	83	-5.2	16.3	133	20.8%	-19.90 [-26.06, -13.74]	
Kano 2015 [12]	-27	16	29	-15	24	74	19.8%	-12.00 [-19.99, -4.01]	
Kaya 2017 [21]	-15.5	13.8	24	-10.1	14.3	28	20.0%	-5.40 [-13.05, 2.25]	
Subtotal (95% CI)			136			235	60.7%	-12.67 [-21.33, -4.02]	$\bullet$
Heterogeneity: Tau <sup>2</sup> =	44.77; 0	Chi² = 8.58, df =	2 (P =	0.01); l <sup>i</sup>	² = 77%				
Test for overall effect:	Z = 2.87	' (P = 0.004)							
11.2.2 Baseline logM	AR BCV	∕A >0.6							
Gharbiya 2018 [28]	-31.5	48.6	38	-9.4	28.8	38	13.5%	-22.10 [-40.06, -4.14]	
Subtotal (95% CI)			38			38	13.5%	-22.10 [-40.06, -4.14]	$\bullet$
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.41	(P = 0.02)							
11.2.3 Other studies									
Kim 2016/2 [17]	-22.8	116.8679169	85	-12.4	104.3529108	155	7.9%	-10.40 [-40.18, 19.38]	
Yun 2016 [18]	25.1	18.3	21	11.6	22.6	33	18.0%	13.50 [2.51, 24.49]	
Subtotal (95% CI)			106			188	25.9%	5.72 [-16.22, 27.67]	
Heterogeneity: Tau <sup>2</sup> =	154.42;	Chi <sup>2</sup> = 2.18, df	= 1 (P :	= 0.14);	l² = 54%				
Test for overall effect:	Z = 0.51	(P = 0.61)							
Total (95% CI)			280			461	100.0%	-8.98 [-19.38, 1.43]	<b>•</b>
Heterogeneity: Tau <sup>2</sup> =	125.47;	Chi <sup>2</sup> = 30.68, d	f = 5 (P	< 0.00	01); l² = 84%				
Test for overall effect:	Z = 1.69	) (P = 0.09)							- 100 - 50 0 50 100
Test for subaroup diffe	erences:	Chi <sup>2</sup> = 3.74. df	= 2 (P =	= 0.15).	l <sup>2</sup> = 46.5%				ravours [experimental] Favours [control]

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 ( $\chi^2 = 2.64\%$ , df = 2, p = 0.27; I<sup>2</sup> = 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  $\mu$ m (95% CI: -73.88 to -13.87; p = 0.004) at 3 months, and by ~34.1  $\mu$ m (95% CI: -76.30 to 8.07; p = 0.11) at 12 months. There was no significant heterogeneity at 3 months ( $\chi^2$  = 0.03, df = 1, p = 0.86; I<sup>2</sup> = 0%) and 12 months ( $\chi^2$  = 1.96, df = 1, p = 0.16; I<sup>2</sup> = 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).

Outcomes of	Studies,	Aflibercept	Ranibizumab	WMD/OR	Р	Study heterogeneity			
interest	no.	Eyes, no.	Eyes, no.	(95% CI)	value	χ²	df	I², %	P value
			Main out	comes					
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 out	comes					
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

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

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  $\mu$ m between two groups could also be considered clinically significant as it translates to ~4.5% difference in thickness, assuming ~278  $\mu$ m 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  $\mu$ m (~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.

# Funding

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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>i.e.</i> , 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.	Supplemen- tary <b>Table S2</b>
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).	Supplemen- tary <b>Table S3</b>
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]	Switzerla nd	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]	Switzerla nd	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).

Chur di an	Select	ion (four s	cores)	Compara	ability (tw	o scores)	Outco	Quality		
Studies –	<b>S</b> 1	S2	<b>S</b> 3	S4	C1	C2	01	O2	O3	score
Hata 2014 [10]	Yes	Yes	Yes	Yes	а	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	с	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