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SYSTEMATIC REVIEW

Efficacy of Intravitreal Anti-VEGF Agents in Neovascular Age-Related Macular Degeneration Patients with or without Polypoidal Choroidal Vasculopathy: A Meta-Analysis

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Abstract

Aims/Background The classification of polypoidal choroidal vasculopathy (PCV) as a subtype of neovascular age-related macular degeneration (nAMD) remained an ongoing controversy. This meta-analysis examines the efficacy of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents in nAMD patients with or without PCV.

Methods A systematic search was conducted in four databases, including PubMed, EMBASE, MEDLINE, and Cochrane Library, from their inception to 1 July 2023. The outcome measure was the change in best-corrected visual acuity (BCVA) and center retinal thickness (CRT) from the baseline to different follow-up durations. Furthermore, sensitivity analysis was performed when significant heterogeneity was detected.

Results This meta-analysis included sixteen studies involving 6679 patients, comprising 5070 non-PCV and 1609 PCV cases. The findings revealed that the improvement in BCVA at 6-month follow-up (mean difference (MD) = 0.05; 95% confidence interval (CI), 0.02 to 0.07; $p = 0.0001$) and the reduction in CRT at 3-month follow-up duration (MD = 10.29; 95% CI, 0.93 to 19.66; $p = 0.03$) were significantly greater in the PCV group compared to the non-PCV group.

Conclusion This meta-analysis indicates that PCV may exhibit better short-term efficacy in response to anti-VEGF therapy than non-PCV.

Systematic Review Registration PROSPERO (CRD42023445591).

Key words: neovascular age-related macular degeneration; polypoidal choroidal vasculopathy; anti-vascular endothelial growth factor; meta-analysis

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Introduction

Age-related macular degeneration (AMD) is a progressively deteriorating condition that can lead to a loss of central vision. It is the primary cause of irreversible blindness among the elderly and ranks among the top five leading causes of blindness worldwide (GBD, 2021; Lim et al, 2012). AMD occurs in two main forms: neovascular and non-neovascular (Li et al, 2020). In the late stages, AMD involves outer retina atrophy, degeneration and thinning of retinal pigment epithelium (RPE),

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and macular neovascularization (MNV). Neovascularization can result in fluid leakage, bleeding, scarring, and severe visual impairment. MNV represents the vascular and associated tissue growth, invading the outer retina, the subretinal, or sub-RPE spaces to varying degrees (Spaide et al, 2020). The neovascularization's anatomical location divides neovascular AMD (nAMD) into subtypes.

Polypoidal choroidal vasculopathy (PCV) is referred to polypoidal expansions originating from the terminal portions of a branching vascular network within the choroid located under the RPE. PCV is generally considered a subtype of AMD and is more prevalent in Asians (Laude et al, 2010; Lim et al, 2010). However, recent insights into understanding its pathogenesis, along with extensive imaging research, indicate that PCV is a subtype of type 1 neovascularization with distinct clinical and radiographic features compared to typical nAMD (Cheung et al, 2018). Therefore, distinguishing AMD types is crucial, and multimodal imaging approaches, such as indocyanine green angiography and optical coherence tomography (OCT), play a vital role in this differentiation.

Currently, the primary treatment for nAMD involves intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, such as bevacizumab, ranibizumab, and aflibercept. Vascular endothelial growth factor (VEGF) is produced in the retina during hypoxia and enhances retinal vascular permeability while promoting neovascularization. Thus, inhibiting VEGF, a crucial angiogenic protein, is an effective approach to treat nAMD (Ferrara, 2004). The treatment strategy for PCV is primarily based on the standard regimen for typical nAMD. In addition to intravitreal anti-VEGF injections, PCV treatment may include focal laser photocoagulation and photodynamic therapy (PDT). While anti-VEGF monotherapy can improve vision in PCV cases, polyp regression rates are limited to about 25–40% (Kang and Koh, 2013; Matsumiya et al, 2013). Combining anti-VEGF injections with PDT provides better visual improvements than anti-VEGF monotherapy in PCV (Qian et al, 2018).

Genetic, proteomic, and imaging studies indicated that the previously established link between PCV and nAMD may need re-evaluated (Wong et al, 2016). Choroidal neovascularization secondary to AMD (CNV-AMD) is the common subtype in Western populations. The lower aqueous levels of VEGF in PCV patients compared to classic AMD suggested that the pathogenesis of PCV may be less dependent on VEGF (Tong et al, 2006). It is crucial to acknowledge that these variations are vital because they result in differences in how PCV and nAMD respond. This means that distinguishing between different types of nAMD holds significant clinical implications (Wong et al, 2016). These differences in pathogenesis may lead to varying treatment options and outcomes for nAMD and PCV. Therefore, accurately diagnosing PCV and distinguishing PCV from other types of nAMD is crucial in effectively managing and promptly treating neovascular diseases.

Methods

Literature Search

This study was pre-registered on PROSPERO (CRD42023445591, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=445591) and adhered to the PRISMA guidelines (Page et al, 2021). The PRISMA checklist is shown in **Supplementary File**. We conducted a comprehensive search across 4 databases (EMBASE, PubMed, MEDLINE, and Cochrane Library) from their initiation until 1 July 2023. To identify relevant manuscripts, we used the following search terms: (macular degeneration OR retinal degeneration) AND (polypoidal choroidal vasculopathy OR PCV) AND (vascular endothelial growth factor OR VEGF OR bevacizumab OR ranibizumab OR aflibercept) AND (clinical trial OR randomized controlled trial). The search was restricted to the studies published in English and the detailed search strategy is provided in the Appendix.

Inclusion and Exclusion of the Relevant Manuscripts

The inclusion criteria for this study were as follows: (1) patients with nAMD, (2) a comparative study design, (3) a comparison of the efficacy of intravitreal anti-VEGF agents in non-PCV or PCV patients, (4) a minimum follow-up period of 3 months, and (5) studies reporting best-corrected visual acuity (BCVA) and center retinal thickness (CRT). However, we excluded the studies with insufficient data, duplicate publications, case reports, review articles, meeting abstracts, or incomplete texts. Moreover, studies on PDT treatment patients and those published in non-English language were also excluded.

Outcome Measures

This study aims to compare the mean changes in BCVA and CRT at various follow-up points (3, 6, 12, and 24 months) between the non-PCV and PCV groups following intravitreal anti-VEGF treatment. For consistent statistical outcomes, all BCVA data were uniformly expressed as the logarithm of the minimum angle of resolution (logMAR) (Khoshnood et al, 2010). During the follow-up period, ocular and systemic adverse events (AEs) and serious adverse events (SAEs) were documented to evaluate treatment safety.

Data Extraction and Quality Assessment

Two independent researchers reviewed the manuscripts and extracted the following data from relevant studies: (1) basic information, such as author name, publication year, study location, and study design, (2) patient information, including age, gender, and diagnosis, (3) treatment details such as use of anti-VEGF, treatment method, follow-up period, and number of injections, and (4) treatment outcomes such as the mean (SD) of BCAV and CRT following treatment at 3, 6, 12, and 24 months and any reported adverse events.

The methodological quality of the included studies was evaluated by two reviewers independently using a modified Newcastle-Ottawa scale (Wells et al, 2021). Each study was rated on a score of 0–9 stars. Studies scoring above 6 stars were

deemed high-quality. All included studies scored above six. In case of any disagreements or discrepancies, we involved a third investigator to achieve a consensus about the included data.

Statistical Analyses

Revman 5.4 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to analyze data and generate forest plots. The findings are described as mean difference (MD) with a 95% confidence interval (CI) for continuous data. Different models were applied based on the significance of statistical heterogeneity. When significant heterogeneity was observed ($I^2 \geq 50\%$), a random effects model was employed; if heterogeneity was not significant ($I^2 < 50\%$), a fixed effect model was used. A p-value of <0.05 was considered statistically significant.

The forest plots depicted the summary MD from all articles included in this analysis. The likelihood of publication bias was evaluated using funnel plots, and sensitivity analysis was performed utilizing the leave-one-out method.

Results

Literature Selection

The process of identifying and selecting studies is presented in Fig. 1, following the PRISMA flowchart guidelines (Page et al, 2021). Initially, 915 manuscripts were first identified through database searches. Of these articles, 233 were excluded due to duplication, and 624 were omitted after reviewing their titles and abstracts. Furthermore, 10 more articles were excluded due to incomplete text. After performing a full-text review, 32 studies were excluded because they addressed inappropriate topics, had no relevant results, or included additional therapeutic strategies for PCV. Finally, this meta-analysis included 16 studies (Azuma et al, 2018; Baba et al, 2012; Calvo-Gonzalez et al, 2019; Ellabban et al, 2012; Hirakata et al, 2016; Kawashima et al, 2015; Kikushima et al, 2017; Kim et al, 2014; Koh et al, 2020; Maruko et al, 2020; Matsumoto et al, 2018; Mukai et al, 2023; Nizawa et al, 2021; Ogasawara et al, 2018; Ryu et al, 2021; Yoon et al, 2021).

Baseline Characteristics

The basic characteristics of 16 included articles are presented in Table 1. In total, 6679 patients were analyzed, including 5070 non-PCV and 1609 PCV cases. The mean patient age ranged from 67.8 to 82.1 years, and the follow-up duration in these studies varied from 1 to 36 months.

The baseline BCVA values exhibited an average range of 0.16 to 1.33 logMAR in the non-PCV group and between 0.06 and 1.41 logMAR in the PCV group. The average baseline CRT values ranged from 214 to 551 μm in the non-PCV group and 182 to 578.2 μm in the PCV group. The mean number of anti-VEFG injections was between 3 and 15.5 times and between 2.68 and 15.1 times for non-PCV and PCV groups, respectively. Furthermore, all studies received a rating of at least 6 stars (Table 2).

Table 1. Baseline characteristics of the 16 included studies in the meta-analysis.

Study	Location	Study design	Treatment	Diagnosis	Number (eye)	Age (y) Mean ± SD	Gender (M/F)	Number of injections	Follow-up (months)
(Azuma et al, 2018)	Japan	Retrospective	IAI (3+TAE)	Typical AMD PCV	22 40	76.4 ± 6.6 74.0 ± 6.8	13/9 30/10	10.3 ± 4.9 10.0 ± 4.2	3, 12, 24
(Baba et al, 2012)	Japan	Retrospective	IVR (3+PRN)/IVB (1+PRN)	Occult CNV PCV	12 14	71.7 ± 5.9 67.8 ± 7.7	9/3 13/1	4.3 ± 2.1 2.7 ± 2.7	24
(Calvo-Gonzalez et al, 2019)	Spain	Prospective	IAI (3+TAE)	Type I CNV PCV	20 12	77.8 ± 5.6 77.6 ± 5.1	8/12 4/8	15.5 ± 3.0 15.1 ± 3.5	3, 12, 24
(Ellabban et al, 2012)	Japan	Prospective	IVR (3+PRN)	AMD PCV	20 20	76.2 ± 6.2 71.7 ± 9.2	15/5 16/4	3.5 ± 0.9 3.9 ± 1.4	3, 8.4 ± 3.7 3, 8.4 ± 3.3
(Hirakata et al, 2016)	Japan	Retrospective	IAI (1+TAE)	Occult CNV PCV	7 7	82.1 ± 11.3 73.3 ± 4.3	5/2 4/3	7.6 ± 1.7 7.9 ± 2.9	1, 3, 6
(Kawashima et al, 2015)	Japan	Prospective	IAI (3+bi-monthly)	AMD PCV	15 26	76.9 ± 8.7 74.8 ± 7.6	13/2 23/3	5 5	6
(Kikushima et al, 2017)	Japan	Retrospective	IAI (3+PRN)	Typical AMD PCV	71 69	78.7 ± 7.4 72.9 ± 7.9	42/29 47/22	N/A N/A	3, 6, 9, 12
(Kim et al, 2014)	Korea	Retrospective	IVR/IVB (1+PRN)	Typical AMD PCV	23 42	N/A N/A	N/A N/A	N/A N/A	6, 12
(Koh et al, 2020)	Global	Prospective	IVR (PRN)	Non-PCV PCV	3093 274	N/A N/A	N/A N/A	5.1 ± 2.7 4.4 ± 2.3	12
(Maruko et al, 2020)	Japan	Prospective	IAI (3+TAE)	Typical AMD PCV	45 49	N/A N/A	N/A N/A	14.3 ± 4.5 12.0 ± 3.0	12, 24
(Matsumoto et al, 2018)	Japan	Retrospective	IAI (3+TAE)	Classic CNV Occult CNV PCV	18 44 58	75.7 71.5 72.4	11/7 37/7 45/13	12.4 14.1 13.3	12, 24

Table 1. Continued.

Study	Location	Study design	Treatment	Diagnosis	Number (eye)	Age (y) Mean ± SD	Gender (M/F)	Number of injections	Follow-up (months)
(Mukai et al, 2023)	Japan	Retrospective	IVF (3)	Type1 and/or 2 MNV PCV	32 22	77.0 ± 9.0 73.0 ± 10.0	22/10 19/3	3 3	3
(Nizawa et al, 2021)	Japan	Prospective	IAI (3+bi-monthly)	Non-PCV PCV	18 19	75.1 ± 6.8 72.1 ± 8.3	12/6 14/5	N/A N/A	3, 6, 12
(Ogasawara et al, 2018)	Japan	Retrospective	IAI (3+bi-monthly)	Typical AMD PCV	45 64	78.0 ± 10.2 72.7 ± 7.5	37/8 48/16	6 6	12
(Ryu et al, 2021)	Korea	Prospective	IAI (PRN)	Non-PCV PCV	1529 825	71.6 ± 9.0 68.9 ± 8.9	921/608 569/256	3.2 ± 1.1 3.4 ± 1.0	1, 2, 3, 4, 5, 6, 7, 8
(Yoon et al, 2021)	Korea	Retrospective	IVR/IAI (3+PRN)	Typical AMD PCV	56 68	73.6 ± 7.3 70.8 ± 7.1	31/25 40/28	13.2 ± 7.4 12.4 ± 7.0	3, 12, 24, 36

M, male; F, female; IAI, intravitreal aflibercept injection; TAE, treat-and-extend; AMD, age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; IVR, intravitreal ranibizumab; IVB, intravitreal bevacizumab; PRN, pro re nata; IVF, intravitreal faricimab; MNV, macular neovascularization; CNV, choroidal neovascularization; SD, standard deviation; N/A, not available.

Table 2. Quality evaluation of the included studies using the Newcastle-Ottawa scale.

Study	Selection			Comparability		Outcome			NOS score
	Representa-tiveness	Selection of the non-exposed	Ascertainment of exposure	Outcome not present at the start	Comparability of most important factors	Comparability on other risk factors	Assessment of outcome	Long enough follow-up (≥1 year)	Adequacy of follow-up	
(Azuma et al, 2018)	*	*	*	*	*	-	*	*	*	8
(Baba et al, 2012)	*	*	*	*	*	-	*	*	*	8
(Calvo-Gonzalez et al, 2019)	*	*	*	*	*	-	*	*	*	8
(Ellabban et al, 2012)	*	*	*	*	-	-	*	-	*	6
(Hirakata et al, 2016)	*	*	*	*	-	-	*	*	*	7
(Kawashima et al, 2015)	*	*	*	*	*	-	*	-	*	7
(Kikushima et al, 2017)	*	*	*	*	-	-	*	*	*	7
(Kim et al, 2014)	*	*	*	*	-	-	*	-	*	6
(Koh et al, 2020)	*	*	*	*	*	-	*	*	-	7
(Maruko et al, 2020)	*	*	*	*	-	-	*	*	*	7
(Matsumoto et al, 2018)	*	*	*	*	-	-	*	*	*	7
(Mukai et al, 2023)	*	*	*	*	*	-	*	-	*	7
(Nizawa et al, 2021)	*	*	*	*	*	*	*	*	*	9
(Ogasawara et al, 2018)	*	*	*	*	*	-	*	*	*	8
(Ryu et al, 2021)	*	*	*	*	-	-	*	-	*	6
(Yoon et al, 2021)	*	*	*	*	*	-	*	*	*	8

*: Achievement of Newcastle-Ottawa Scale score requirements; -: Failure to achieve score requirements. NOS, Newcastle-Ottawa scale.

Best-Corrected Visual Acuity

Fig. 2 illustrates the changes in BCVA from the baseline to the different follow-up time points (3, 6, 12, and 24 months). The average improvement in BCVA from the baseline to 3 months was assessed across 10 articles, indicating no significant distinctions between the groups, with a variation of 0.01 logMAR (95% CI, –0.01 to 0.04; $p = 0.27$; $I^2 = 0\%$) (Fig. 2A). At 6 months, data from 6 studies revealed that BCVA improvements were significantly greater in the PCV group, with a change of 0.05 logMAR (95% CI, 0.02 to 0.07; $p = 0.0001$, $I^2 = 26\%$) (Fig. 2B). We compared the average change in BCVA after 12 months based on 10 studies, the findings demonstrated an insignificant difference of 0.02 logMAR (95% CI, –0.01 to 0.05; $p = 0.24$; $I^2 = 0\%$) (Fig. 2C). Finally, comparing the mean change in BCVA at 24 months across 6 studies indicated no substantial variations, with a change of 0.02 logMAR (95% CI, –0.04 to 0.09; $p = 0.45$; $I^2 = 9\%$) (Fig. 2D).

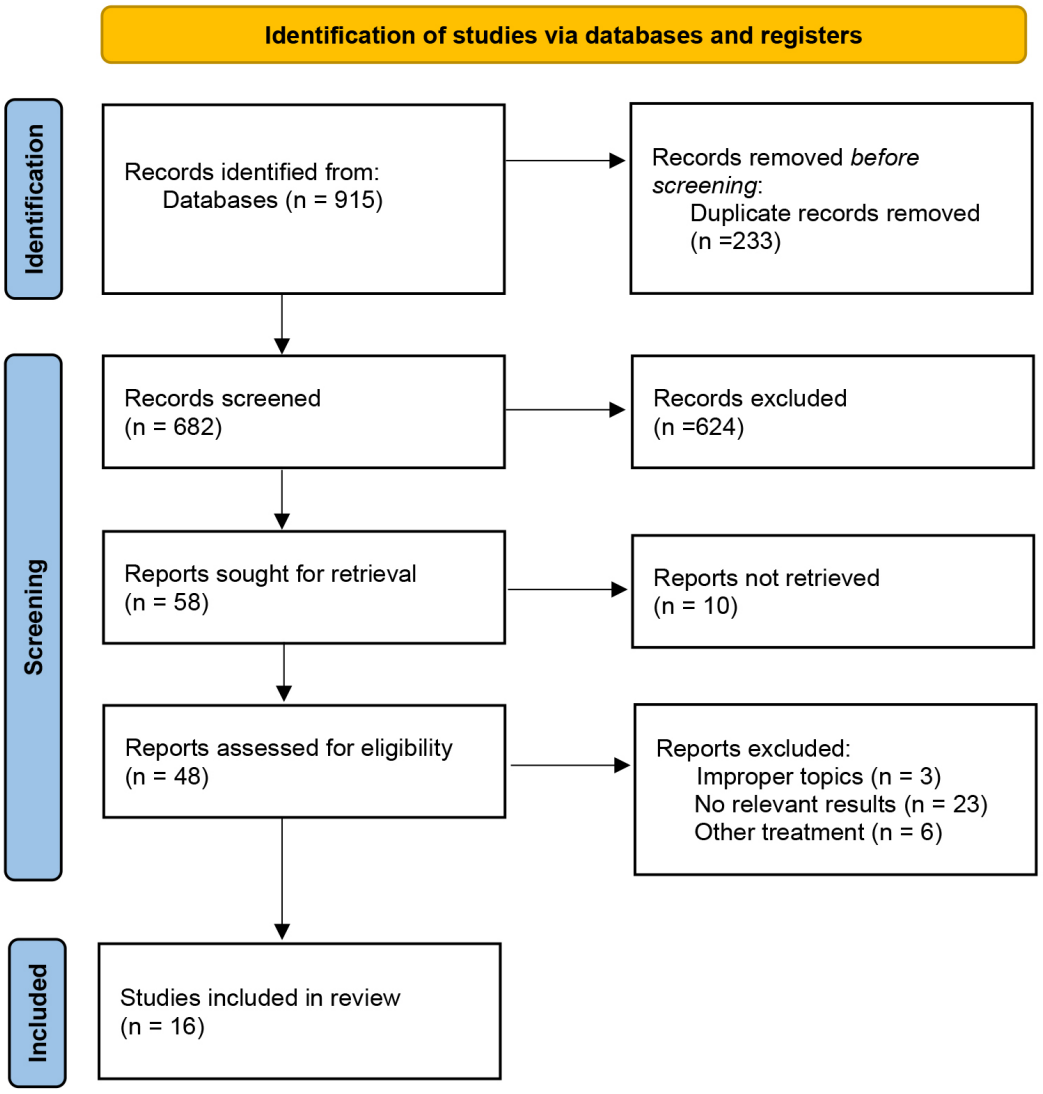

Fig. 1. A flowchart of identifying and selecting relevant studies.

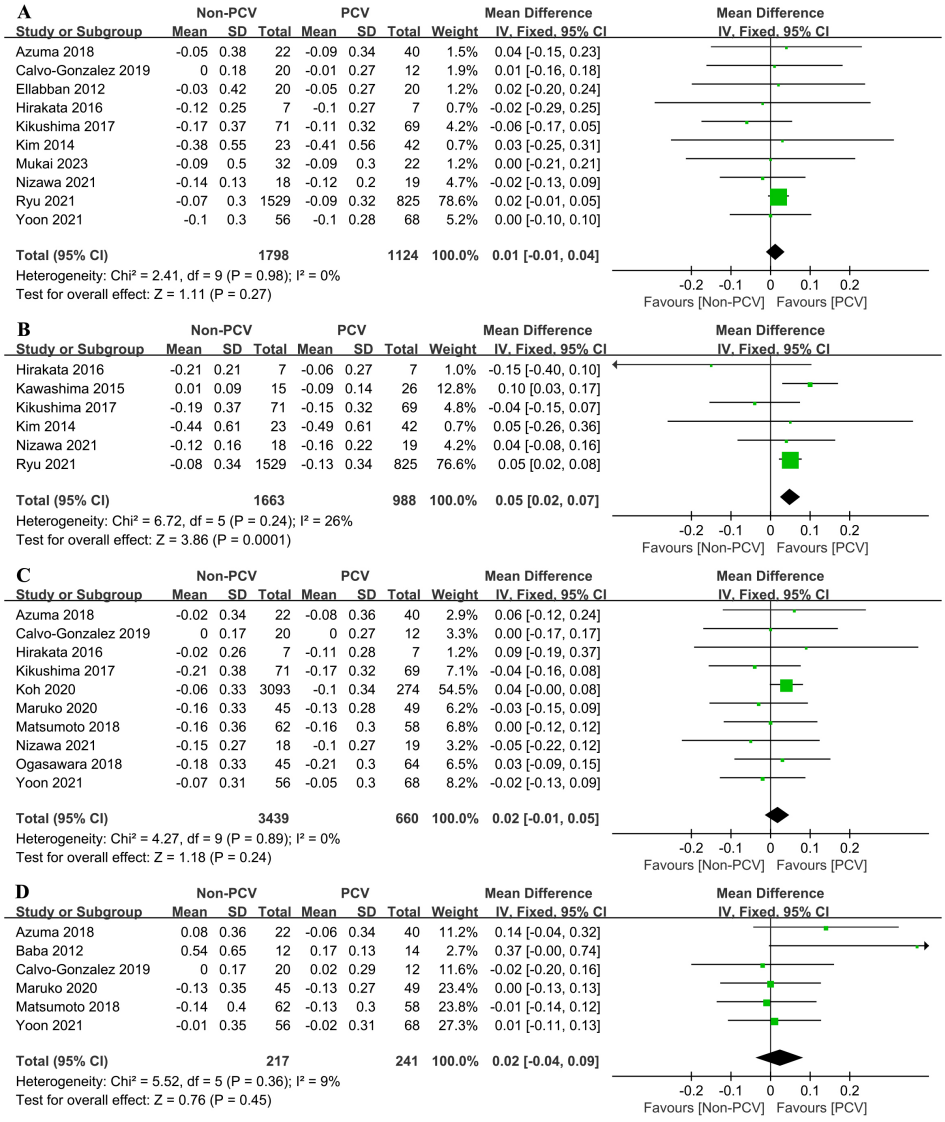

Fig. 2. Forest plot of best-corrected visual acuity. (A) 3-month follow-up. (B) 6-month follow-up. (C) 12-month follow-up. (D) 24-month follow-up. PCV, polypoidal choroidal vasculopathy; IV, inverse-variance; SD, standard deviation; CI, confidence interval.

Center Retinal Thickness

A comparison of the mean reduction in CRT between the two groups at 3, 6, 12, and 24 months from baseline is shown in Fig. 3. Analysis of 10 studies performed over a 3-month follow-up period indicated the MD of 10.29 μm in CRT reduction between the two groups (95% CI, 0.93 to 19.66; $p = 0.03$; $I^2 = 45\%$) (Fig. 3A). However, at a 6-month follow-up period, results from 6 studies showed no significant difference in CRT between the two groups, with a mean change of 2.93 μm (95% CI, –29.74 to 35.60; $p = 0.86$; $I^2 = 66\%$) (Fig. 3B). Moreover, comparing 10 studies over a 12-month follow-up period indicated a MD of –8.00 μm (95% CI, –32.13 to 16.14; $p = 0.52$; $I^2 = 57\%$) (Fig. 3C). Additionally, at 24 months, the MD in CRT reduction between the two groups across 6 studies were –7.39 μm (95% CI, –28.31 to 13.54; $p = 0.49$; $I^2 = 0\%$) (Fig. 3D).

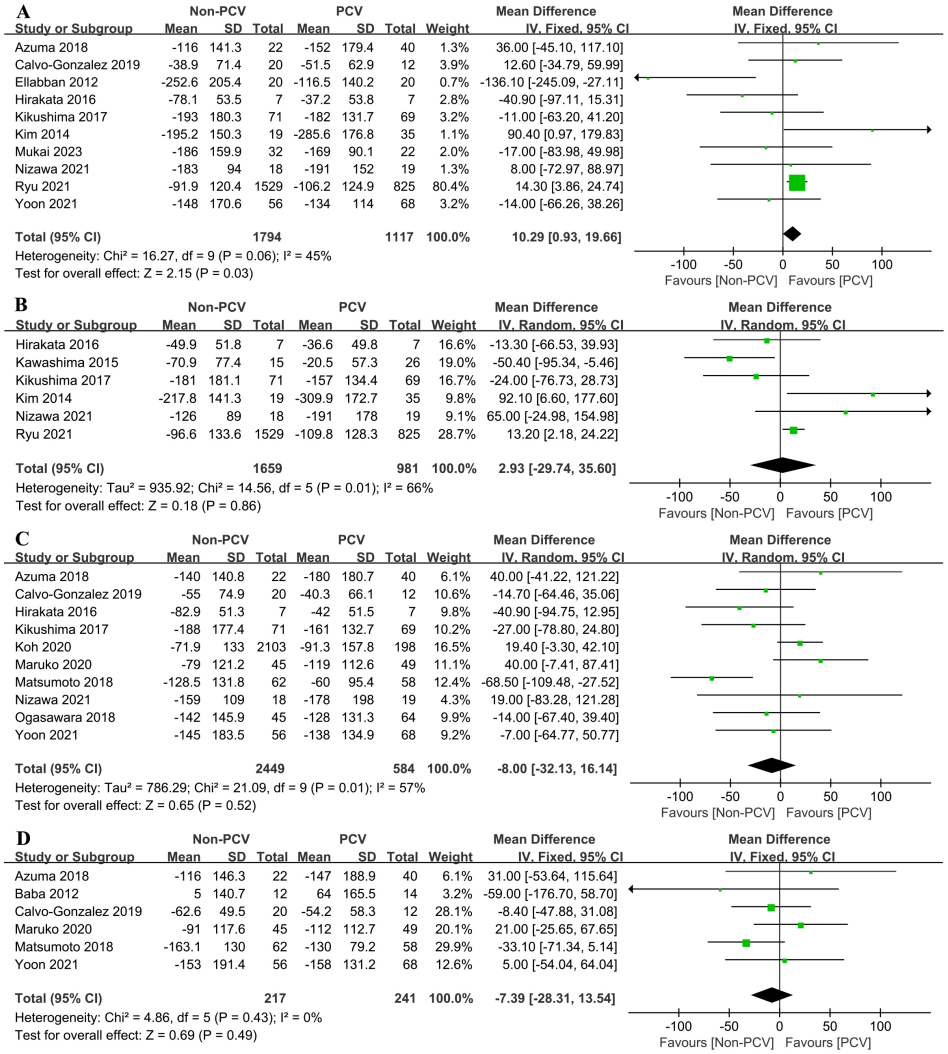

Fig. 3. Forest plot of center retinal thickness. (A) 3-month follow-up. (B) 6-month follow-up. (C) 12-month follow-up. (D) 24-month follow-up. PCV, polypoidal choroidal vasculopathy; IV, inverse-variance; SD, standard deviation; CI, confidence interval.

Based on the significant heterogeneity observed in 6 and 12 months, we used the leave-one-out method to determine sensitivity. It was found that after excluding the study by Kawashima et al (2015), the heterogeneity in CRT decreased for 6-month follow-up period. However, re-evaluating the data revealed a significantly larger enhancement in CRT in the PCV group (MD = 12.6; 95% CI, 2.17 to 23.02; $p = 0.02$; $I^2 = 46\%$) (**Supplementary Fig. 1**). Similarly, in the 12-month follow-up, excluding the study by Matsumoto et al (2018) significantly reduced heterogeneity, and re-evaluation of the data showed that the results remained unchanged (MD = 5.95; 95% CI, –9.12 to 21.02; $p = 0.44$; $I^2 = 19\%$) (**Supplementary Fig. 2**). A subgroup analysis of the 12-month follow-up was performed, but there was no significant reduction in heterogeneity when assessing based on different drugs (**Supplementary Fig. 3**).

Publication Bias

Publication bias was evaluated using a funnel plot analysis involving ten studies. The results indicated that the funnel plot was not entirely symmetrical (**Supplementary Fig. 4**), suggesting the presence of potential publication bias. We performed subgroup analyses based on country, study type, medication regimen, and drug differences for analyses including more than ten studies. These analyses showed no significant differences in heterogeneity or comparative outcomes.

Safety

The included studies demonstrated serious ocular adverse events, including severe vitreous hemorrhage, retinal hemorrhage, RPE tears, endophthalmitis, and macular holes. Other eye-related AEs included dry eye, increased intraocular pressure, cataracts, conjunctival hemorrhage, and vitreous floaters. Furthermore, several serious systemic adverse events were also reported.

Discussion

The categorization of PCV as a subtype of nAMD remains a topic of ongoing debate (Laude et al, 2010). Hence, this review aims to provide a comprehensive comparison of the effectiveness and safety of intravitreal anti-VEGF treatment between non-PCV and PCV eyes. BCVA serves as a key means of assessing the therapeutic effect, while CRT is an important indicator of anatomical outcomes.

Our finding demonstrated that at a 3-month follow-up, individuals receiving anti-VEGF treatment for PCV showed a significant reduction in CRT compared to non-PCV therapy. In the 6-month follow-up, after excluding a study by Kawashima et al (2015), the heterogeneity in CRT outcomes decreased, and a re-evaluation indicated that the improvement in CRT was more pronounced within the PCV group. Furthermore, BCVA changes were more significant for PCV at 6 months. However, at other follow-up intervals, no significant difference was observed in BCVA gains or CRT decrease between the two groups. These findings imply that anti-VEGF monotherapy might be more effective in treating PCV than non-PCV, particularly within a period of less than 6 months. However, when considering long-term outcomes, the efficacy seems similar between these two treatment groups. Additionally, our study revealed a higher tendency for PCV to impact younger individuals, which is consistent with the findings of previous research (Zhalka et al, 2022).

There was significant heterogeneity in the results of CRT at 6- and 12-month follow-up (I^2 = 66%, I^2 = 57%). It was found that after excluding a study published by Kawashima et al (2015), the heterogeneity of CRT decreased at 6 months follow-up (I^2 = 46%), and the improvement in CRT was significantly better in PCV compared to the non-PCV group (MD = 12.6; 95% CI, 2.17 to 23.02; p = 0.02). Considering the possibility that participants were those who switched to aflibercept after 6 months of poor efficacy with ranibizumab, the total treatment duration will be 12 months. Moreover, excluding a study by Matsumoto et al (2018) in the 12-month follow-up of CRT significantly reduced heterogeneity (I^2 = 19%), and a re-evaluation of the data showed that the results remained unchanged. Mat-

sumoto's study used OCT to diagnose PCV rather than indocyanine green angiography (ICGA) which might have biased the findings.

PCV has a higher prevalence of serous retinal detachment and is more prone to hemorrhage and massive macular hemorrhage compared to eyes with typical nAMD (Ozawa et al, 2009). In terms of safety, some of the included studies reported serious eye adverse events, with some of these cases requiring vitrectomy due to severe vitreous bleeding. Koh et al (2020)'s study demonstrated a somewhat higher incidence of retinal and vitreous hemorrhage in the PCV group than in the non-PCV group. However, the incidence of ocular and systemic AEs and SAEs was slightly elevated in the non-PCV group than in the PCV group. The overall rate of ocular AEs was 6.5% in the PCV group and 8.4% in the non-PCV group (Koh et al, 2020). There was one patient with retinal pigment epithelium tear in both groups in Mukai et al (2023)'s research.

The two studies conducted by Koh et al (2020) and Ryu et al (2021) were real-world analyses with large sample sizes that utilized an as-needed (pro re nata (PRN)) protocol for anti-VEGF therapy, resulting in fewer injections throughout the treatment course. Long-term vision improvement can be affected by treatment regimen and injection frequency. In Koh et al (2020)'s study, the average number of injections was 3.9 ± 2.3 for non-PCV patients and 4.2 ± 1.9 for PCV cases, while Ryu et al (2021)'s study reported 3.2 ± 1.1 and 3.4 ± 1.0 for non-PCV and PCV patients, respectively. Monthly or PRN dosing regimens of intravitreal anti-VEGF have been established as effective therapies for nAMD. Furthermore, the treat-and-extend (T&E) strategy is being adopted in clinical practice as it reduces the treatment burden by extending injection intervals when appropriate. A study conducted by Huang et al (2024) reported that the T&E regimen was effective for treating nAMD, with an average of 10.95 injections over 2 years, indicating improved anatomy and function (Huang et al, 2024). The T&E and fixed dosing schedule was retinoprotective, with T&E patients achieving better visual acuity outcomes than the PRN method. While both T&E and PRN reduced the number of injections to one year, the T&E method needed injections more frequently (Rosenberg et al, 2023; Rufai et al, 2017).

Both PCV and nAMD are considered to result from abnormal vascular lesions involving the choroidal vascular system, with potential recurrence of serous exudation and hemorrhages (Laude et al, 2010). However, it is crucial to distinguish PCV from typical nAMD. These two conditions exhibit different natural histories, demographics, imaging features, and clinical presentations, as described in several studies (Sho et al, 2003; Tan et al, 2016; Terasaki et al, 2002). VEGF is produced by retinal pigment epithelial cells, vascular endothelial cells, and glial cells (Stone et al, 1995; Yi et al, 1998), and increased VEGF levels in the aqueous humor are linked to AMD-related diseases (Tong et al, 2006). Considering the link between VEGF and neovascularization, intravitreal anti-VEGF therapy has become a standard treatment approach for nAMD.

VEGF has been implicated in PCV, but its exact role in the disease is yet to be explored. Some studies have revealed high VEGF expression in vascular endothelial and RPE cells (Matsuoka et al, 2004; Terasaki et al, 2002), while others

have found no significant VEGF expression (Nakashizuka et al, 2008). Some studies have indicated that the VEGF levels in the aqueous humor of PCV patients are higher than the normal levels and lower than those observed in typical nAMD (Lee et al, 2013; Tong et al, 2006). Intravitreal anti-VEGF injections have been found to decrease retinal edema and subretinal fluid and restore macular morphology and vision (Golbaz et al, 2011). Our analysis further indicated that anti-VEGF treatment of PCV is equally effective as for nAMD, with even better short-term outcomes. Therefore, these observations suggest that anti-VEGF treatment may be highly effective for PCV.

Furthermore, significant associations have been observed between increased levels of pro-inflammatory cytokines, including interleukin-1b and interleukin-23, and PCV, suggesting that inflammatory processes are linked to the development of PCV (Sasaki et al, 2012; Zhao et al, 2015). While AMD causes most type 1 neovascularization, a study suggests that pachychoroid disease may also lead to type 1 neovascularization (Pang and Freund, 2015). Studies using enhanced depth OCT have observed choroid thickening in patients with PCV, compared to the thinner choroid observed in AMD (Koizumi et al, 2011). At the site of polypoidal disease, the choroid thickens, and these changes are topographically linked to the location of new blood vessel formation (Yamashiro et al, 2022). It suggested that PCV may belong to the pachychoroid disease spectrum, involving different pathogenic mechanisms compared to nAMD (Pang and Freund, 2015).

Therefore, our study compared the effectiveness of anti-VEGF monotherapy for PCV and other types of AMD that do not involve PCV. Our findings indicate that short-term anti-VEGF monotherapy may be more effective for PCV than non-PCV. This difference may be due to the presence of multiple branch vascular networks in PCV, which is characterized by neovascularization. In the future, classifications of AMD and PCV are expected to be more comprehensive, and precise disease identification will improve treatment possibilities.

However, this meta-analysis has several limitations. Firstly, the articles included are limited by the lack of randomized controlled trials (RCTs). Secondly, the weight given to the analyses of some articles varies widely. Therefore, to improve the quality of future analysis, additional trials with different follow-up durations and larger-sample sizes of RCTs will be needed. Lastly, there was significant heterogeneity in some follow-up durations.

Conclusion

In summary, our analysis revealed that anti-VEGF monotherapy is more effective for PCV than the non-PCV group, with better anatomical outcomes at the 3-month follow-up and functional improvement at the 6-month follow-up period. PCV may show higher short-term efficacy in response to anti-VEGF therapy than non-PCV. Moreover, further research is needed to validate these findings and improve their clinical implementation.

Key Points

- The classification of PCV as a subtype of nAMD remained controversial.
- Some studies indicate that the lower levels of VEGF found in PCV may suggest its pathogenesis is less dependent on VEGF.
- This differentiation could lead to different treatment options and outcomes for nAMD and PCV.
- We observed that by month 6, the improvement in BCVA was significantly greater in the PCV group compared to the non-PCV group.
- Furthermore, at the 3-month follow-up, the decrease in CRT was greater in the PCV group than in the non-PCV group.
- Our study suggests that PCV may show better short-term efficacy in response to anti-VEGF drug therapy compared to the non-PCV group.

Availability of Data and Materials

The datasets used and/or analyzed during the current study were available from the corresponding author.

Author Contributions

LYW and JGD designed the study. LYW and CL searched and selected literature. LYW, SYL, TTH, and CL collected and analyzed the data. LYW participated in drafting the manuscript and all authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0673.

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Appendix

Appendix: Example Search Strategies

Database: Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Polypoidal Choroidal Vasculopathy] explode all trees

#2 (Choroidal Vasculopathies, Polypoidal or Choroidal Vasculopathy, Polypoidal or Polypoidal Choroidal Vasculopathies or Vasculopathy, Polypoidal Choroidal or Polypoidal Choroidal Neovascularization or Choroidal Neovascularization, Polypoidal or Choroidal Neovascularizations, Polypoidal or Neovascularization, Polypoidal Choroidal or Polypoidal Choroidal Neovascularizations or Polypoidal CNV or CNV, Polypoidal or Polypoidal CNVs or Idiopathic Polypoidal Choroidal Vasculopathy or type1 choroidal neovascularization) (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Macular Degeneration] explode all trees

#5 MeSH descriptor: [Retinal Degeneration] explode all trees

#6 MeSH descriptor: [Retinal Neovascularization] explode all trees

#7 MeSH descriptor: [Choroidal Neovascularization] explode all trees

#8 MeSH descriptor: [Macula Lutea] explode all trees

#9 maculopath*

#10 (macula* or retina* or choroid*) near/3 degenerat*

#11 (macula* or retina* or choroid*) near/3 neovascul*

#12 macula* near/2 lutea

#13 AMD or AMRD or CNV

#14 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 #3 and #14

#16 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees

#17 MeSH descriptor: [Angiogenesis Inducing Agents] explode all trees

#18 MeSH descriptor: [Endothelial Growth Factors] explode all trees

#19 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees

#20 anti near/2 VEGF*

#21 anti near/1 angiogen*

#22 endothelial near/2 growth near/2 factor*

#23 (macugen* or pegaptanib* or lucentis* or rhufab* or ranibizumab* or bevacizumab* or avastin* or aflibercept* or conbercept* or OPT 302 or Opthea* or RTH258 or Brolucizumab* or abicipar pegol)

#24 VEGF TRAP*
#25 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26 #15 and #25

Database: Embase (OVID)

1 exp Polypoidal Choroidal Vasculopathy/
2 "polypoidal choroidal vasculopathy".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
3 exp retina macula degeneration/
4 exp retinal degeneration/
5 exp subretinal neovascularization/
6 maculopath$.tw.
7 ((macul$ or retina$ or choroid$) adj3 degener$).tw.
8 ((macul$ or retina$ or choroid$) adj3 neovasc$).tw.
9 (macula$ adj2 lutea).tw.
10 (AMD or ARMD or CNV).tw.
11 or/1-2
12 or/3-10
13 11 and 12
14 angiogenesis/
15 exp angiogenesis inhibitors/
16 angiogenic factor/
17 endothelial cell growth factor/
18 monoclonal antibody/
19 vasculotropin/
20 (anti adj2 VEGF$).tw.
21 (endothelial adj2 growth adj2 factor$).tw.
22 (anti adj1 angiogen$).tw.
23 (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or Brolucizumab$ or abicipar pegol).tw.
24 VEGF TRAP$.tw.
25 or/14-24
26 13 and 25
27 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
28 (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
29 Multicenter Study.pt.
30 Clinical Studies as Topic/
31 exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp"Clinical Trial (topic)"/
32 Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/

33 Randomization/
34 Random Allocation/
35 Double-Blind Method/
36 Double Blind Procedure/
37 Double-Blind Studies/
38 Single-Blind Method/
39 Single Blind Procedure/
40 Single-Blind Studies/
41 Placebos/
42 Placebo/
43 Control Groups/
44 Control Group/
45 Cross-Over Studies/ or Crossover Procedure/
46 (random* or sham or placebo*).ti,ab,hw,kf.
47 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
48 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
49 (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
50 (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
51 (Nonrandom* or non random* or non-random* or quasi-random* or quasir-andom*).ti,ab,hw,kf.
52 (phase adj3 (study or studies or trial*)).ti,ab,hw,kf.
53 ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.
54 ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
55 allocated.ti,ab,hw.
56 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
57 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
58 (pragmatic study or pragmatic studies).ti,ab,hw,kf.
59 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
60 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
61 trial.ti,kf.
62 or/27-61
63 exp animals/
64 exp animal experimentation/
65 exp models animal/
66 exp animal experiment/
67 nonhuman/
68 exp vertebrate/
69 or/63-68
70 exp humans/
71 exp human experiment/
72 or/70-71
73 69 not 72
74 62 not 73

75 26 and 74

Database: MEDLINE (PubMed)

#1 "Polypoidal Choroidal Vasculopathy"[Mesh] OR Choroidal Vasculopathies, Polypoidal or Choroidal Vasculopathy, Polypoidal or Polypoidal Choroidal Vasculopathies or Vasculopathy, Polypoidal Choroidal or Polypoidal Choroidal Neovascularization or Choroidal Neovascularization, Polypoidal or Choroidal Neovascularizations, Polypoidal or Neovascularization, Polypoidal Choroidal or Polypoidal Choroidal Neovascularizations or Polypoidal CNV or CNV, Polypoidal or Polypoidal CNVs or Idiopathic Polypoidal Choroidal Vasculopathy or type1 choroidal neovascularization

#2 "Macular Degeneration"[Mesh] OR Degeneration, Macular or Macular Degenerations or Maculopathy or Maculopathies or Macular Dystrophy or Dystrophy, Macular or Macular Dystrophies or Age-Related Macular Degeneration or Age Related Macular Degeneration or Age-Related Macular Degenerations or Macular Degeneration, Age-Related or Macular Degeneration, Age Related or Maculopathies, Age-Related or Maculopathy, Age-Related or Maculopathy, Age Related or Age-Related Maculopathies or Age Related Maculopathies or Age-Related Maculopathy or Age Related Maculopathy

#3 "Retinal Degeneration"[Mesh] OR Degeneration, Retinal or Degenerations, Retinal or Retinal Degenerations

#4 "Retinal Neovascularization"[Mesh] OR Neovascularization, Retinal or Sea Fan Neovascularization or Neovascularization, Sea Fan or Sea Fan Neovascularizations or Optic Disc Neovascularization or Optic Disc Neovascularizations or Neovascularization, Optic Disc or Optic Disk Neovascularization or Disk Neovascularization, Optic or Neovascularization, Optic Disk or Optic Disk Neovascularizations

#5 "Choroidal Neovascularization"[Mesh] OR Neovascularization, Choroid or Neovascularization, Choroidal or Choroidal Neovascularizations or Choroid Neovascularization or Choroid Neovascularizations

#6 "Macula Lutea"[Mesh] OR Lutea, Macula or Luteas, Macula or Macula Luteas

#7 #2 or #3 or #4 or #5 or #6

#8 #1 and #7

#9 "Angiogenesis Inhibitors"[Mesh] or Angiogenesis Inhibitor or Inhibitor, Angiogenesis or Angiogenetic Antagonist or Antagonist, Angiogenetic or Angiogenetic Antagonists or Antagonists, Angiogenetic or Angiogenetic Inhibitor or Inhibitor, Angiogenetic or Angiogenetic Inhibitors or Angiogenic Antagonists or Angiogenic Antagonist or Antagonist, Angiogenic or Angiogenic Inhibitor or Inhibitor, Angiogenic or Angiostatic Agent or Agent, Angiostatic or Anti-Angiogenetic Agent or Agent, Anti-Angiogenetic or Anti Angiogenetic Agent or Angiogenic Inhibitors or Angiostatic Agents or Agents, Angiostatic or Antagonists, Angiogenic or Anti-Angiogenetic Agents or Agents, Anti-Angiogenetic or Anti Angiogenetic Agents or Anti-Angiogenic Drugs or Anti Angiogenic Drugs or Drugs, Anti-Angiogenic or Antiangiogenic Agents or Agents, Antiangiogenic or Inhibitors, Angiogenesis or Inhibitors, Angiogenetic or Inhibitors, Angiogenic or Inhibitors, Neovascularization or Neovascularization Inhibitors or Anti-Angiogenic Drug or Anti Angio-

genic Drug or Drug, Anti-Angiogenic or Neovascularization Inhibitor or Inhibitor, Neovascularization or Antiangiogenic Agent or Agent, Antiangiogenic or Angiogenesis Factor Inhibitors or Factor Inhibitors, Angiogenesis or Inhibitors, Angiogenesis Factor or Angiogenesis Factor Inhibitor or Factor Inhibitor, Angiogenesis or Inhibitor, Angiogenesis Factor or Anti-Angiogenesis Effect or Anti Angiogenesis Effect or Effect, Anti-Angiogenesis or Antiangiogenesis Effect or Effect, Antiangiogenesis or Antiangiogenesis Effects or Effects, Antiangiogenesis or Anti-Angiogenesis Effects or Anti Angiogenesis Effects or Effects, Anti-Angiogenesis

#10 "Angiogenesis Inducing Agents"[Mesh] OR Agents, Angiogenesis Inducing or Inducing Agents, Angiogenesis or Angiogenesis Stimulating Agents or Agents, Angiogenesis Stimulating or Stimulating Agents, Angiogenesis or Angiogenesis Stimulators or Stimulators, Angiogenesis or Angiogenesis Inducers or Inducers, Angiogenesis or Angiogenesis Factor or Factor, Angiogenesis or Angiogenic Factor or Factor, Angiogenic or Tumor Angiogenic Factor or Angiogenic Factor, Tumor or Factor, Tumor Angiogenic or Angiogenesis Effect or Effect, Angiogenesis or Angiogenesis Effects or Effects, Angiogenesis

#11 "Endothelial Growth Factors"[Mesh] OR Growth Factors, Endothelial or Endo-GF or Endothelial Growth Factor Polypeptides or Endothelial Growth Factor or Growth Factor, Endothelial or ECDGF or Endothelial Cell-Derived Growth Factors or Endothelial Cell Derived Growth Factors or beta-Endothelial Growth Factor or Growth Factor, beta-Endothelial or beta Endothelial Growth Factor or alpha-Endothelial Growth Factor or Growth Factor, alpha-Endothelial or alpha Endothelial Growth Factor

#12 "Vascular Endothelial Growth Factors"[Mesh] OR VEGFs

#13 #9 or #10 or #11 or #12

#14 #8 AND #13

#15 (("Clinical Trial"[PT] OR "Comparative Study"[PT] OR "Evaluation study"[PT] OR "Cross-Over Studies"[MeSH] OR "Clinical Trials as Topic"[MeSH] OR random*[TIAB] OR controll*[TIAB] OR "intervention study"[TIAB] OR "experimental study"[TIAB] OR "comparative study"[TIAB] OR trial[TIAB] OR trials[TIAB] OR evaluat*[TIAB] OR repeat*[TIAB] OR compar*[TIAB] OR versus[TIAB] OR "before and after"[TIAB] OR "interrupted time series"[TIAB]) NOT ("Animals"[MeSH] NOT (Animals[MeSH] AND "Humans"[MeSH])))

#16 "Epidemiologic Studies"[MeSH] OR "case control"[TIAB] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR longitudinal[TIAB] OR retrospective[TIAB] OR "cross sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB]

#17 #15 OR #16

#18 #14 AND #17