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Review article

Enhancing anti-vascular endothelial growth factor with photodynamic therapy for polypoidal choroidal vasculopathy: A meta-analysis

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ABSTRACT

Anti-vascular endothelial growth factor (anti-VEGF) agents administered as either monotherapy or combination with verteporfin photodynamic therapy (PDT) are the 2 dominant treatment for polypoidal choroidal vasculopathy (PCV); however, controversies remain due to small sample sizes and inconsistency in prognosis from randomized controlled trials (RCTs). In accordance with the PRISMA statement, we investigated the efficacy of PDT plus anti-VEGF combination with anti-VEGF monotherapy. This study was accepted by the International Prospective Register of Systematic Reviews (CRD42023471362). Studies published up to July, 2024, were retrieved from PubMed, Embase, and Cochrane databases. A total of 7 RCTs with 926 eyes were reviewed. In 6 trials, combination therapy showed significantly higher rate of complete polyp regression (risk ratio [RR]: 1.56, 95 % CI: 1.15–2.13, $p = 0.005$). In 5 trials, combination therapy also significantly reduced the number of anti-VEGF injections (SMD: -0.65 , 95 % CI: -0.95 to -0.35 , $p < 0.0001$). For best corrected visual acuity improvement, central retinal thickness reduction, and rate of ocular adverse events, the performance of the 2 modalities were comparable. We conclude that PDT plus anti-VEGF combination therapy constitutes a safe and effective modality and should be considered the first-line treatment for PCV.

1. Introduction

Polypoidal choroidal vasculopathy (PCV) is considered to be a type of neovascular age-related macular degeneration (nAMD).³ PCV occurs in approximately 0.3 % of the general population and 60 % of people with nAMD.² It typically presents with declined unilateral visual acuity between ages 50 and 70 years. The characteristics of PCV include aneurysmal polypoidal lesions and branching vascular networks,¹⁹ which frequently cause vitreous hemorrhage, retinal pigment epithelial detachment, and cystoid macular edema. These pathologic characteristics are best observed with indocyanine green angiography.

PCV treatment initially focused on polypoidal lesions. Modalities, such as focal laser or verteporfin photodynamic therapy (PDT),^{21,26} have been widely implemented. Since the revolutionary introduction of anti-vascular endothelial growth factor (anti-VEGF) injections to treat

nAMD and its subtypes, PCV has become the focus of numerous studies.^{9, 11,14} Anti-VEGF agents administered as either monotherapy or combination with verteporfin PDT are currently considered to be the two dominant modalities for PCV treatment.^{10,24} Anti-VEGF monotherapy has demonstrated promising results in improving visual acuity whereas treatment in combination with PDT facilitates polyp regression. Controversies remain due to mainly small sample sizes and single-center studies, uncertainty about the polypoidal recurrence rate,⁷ and inconsistency in reported prognosis from randomized controlled trials.^{8,13} Furthermore, effective PCV management requires multiple anti-VEGF injections and frequent follow-up visits, which could intensify the treatment burden and reduce patient compliance. Therefore, the optimal PCV treatment remains uncertain.

Hence, the objective of this systematic review and meta-analysis is to compare the efficacy of PDT plus anti-VEGF combination therapy with

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anti-VEGF monotherapy as treatment strategies for patients with PCV.

2. Methods

2.1. Data sources

We retrieved relevant studies from PubMed, Embase, and Cochrane databases that were published from the inception of the databases to July 31, 2024, irrespective of language. We used the following search terms and medical subject headings in various combinations: “verteporfin,” “photodynamic therapy,” “anti-VEGF,” “ranibizumab,” “aflibercept,” “bevacizumab,” and “polypoidal choroidal vasculopathy.” Further, we manually searched reference sections of retrieved studies and contacted known researchers with relevant expertise. The systematic review and meta-analysis demonstrated herein was accepted by the online PROSPERO International Prospective Register of Systematic Reviews of the National Institute for Health Research (CRD42023471362).

2.2. Study selection

In order to reduce risks of bias and to effectively examine the cause-effect relationships between the intervention and outcome within the scope of our study, we decided to include only randomized controlled trials (RCT) in the current study. As a result, we included RCTs that compare verteporfin-based PDT plus anti-VEGF combination therapy with anti-VEGF monotherapy that involved patients with PCV of any severity while clearly describing patient selection, inclusion and exclusion criteria. We excluded studies and trials based on the following criteria: designed as nonrandomized or observational trials, assessed overlapping patient cohorts in two or more studies with identical outcomes, or not published as full-text articles in peer-reviewed scientific journals.

2.3. Data extraction and quality assessment

We initially screened selected articles based on titles and abstracts. We then retrieved the full versions of potentially eligible studies for further assessment. Two independent reviewers (THL and PCT) assessed trials for inclusion and extracted the data using a standardized procedure. A third reviewer (HYL) assisted in resolving discrepancies and disagreements. We contacted the trial authors for additional information as needed. Data on the study design (e.g., inclusion and exclusion criteria, randomization), sample characteristics (e.g., sample diagnosis, age, size), experimental and control treatments (e.g., PDT laser fluence, anti-VEGF dosage, program duration, frequency) and reported outcomes were extracted.

THL performed the risk-of-bias analysis for the included trials, considering the following factors: adequacy of randomization, concealment of allocation, deviation from intended interventions, numbers of dropouts, and performance based on an intention-to-treat analysis. The revised Cochrane risk-of-bias tool for randomized trials version 2 was used to rank risk. Funnel plots could not be used to assess publication bias because of the insufficient power of the tool’s tests to determine true asymmetry if fewer than 10 studies are included.⁵

2.4. Data synthesis and analysis

We assessed studies that investigate PDT plus anti-VEGF combination therapy and anti-VEGF monotherapy in separate meta-analyses. Subgroups were introduced to observe the efficacy of treatments in the short (≤ 12 months) and long (> 12 months) terms. Our primary outcomes include the complete polyp regression rate and the number of anti-VEGF injections. The secondary outcomes include best corrected visual acuity (BCVA) improvement, central retinal thickness (CRT) reduction, and ocular adverse rate. We calculated standardized mean differences (SMDs) by dividing the between-group mean differences by

the pooled standard deviations, while risk ratios (RRs) were obtained by dividing the cumulative incidence in the experimental (combination therapy) group by that in the control (monotherapy) group. Further, we computed 95 % confidence intervals (CIs) for these values. We used the Review Manager statistical package (version 5.4; Cochrane Collaboration, Oxford, England), running on an Intel® Core™ i7–7700HQ processor, to conduct all analyses. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses or Statement Guidelines.¹⁸ Chi-square statistics (Q-statistic) and I^2 tests were used to assess heterogeneity across the RCTs.

3. Results

3.1. Characteristics of RCTs

Our initial search yielded 713 papers, of which 288 were duplicates and were excluded (Fig. 1). Screening excluded 327 papers that were judged to be irrelevant. Of the 98 remaining articles, 91 failed to meet the inclusion criteria and were excluded. Therefore, 7 studies were eligible for our meta-analysis.^{9,12,14,15,17,20,25}

Publication dates spanned from 2012 to 2022 with sample sizes of 16–168 and follow-up durations of 20–96 weeks (Table 1). All trials except one¹⁴ included the criterion of using PDT therapies as rescue or pro re nata therapy. All 7 trials have included Institutional Review Board statements in their “Methods” section, and they all adhered to the tenets of the Declaration of Helsinki, with informed consent obtained from all patients.

3.2. Risk of bias

Most risks of bias were low, but the risk ranking was “some concerns” for certain factors in 4r trials^{12,14,20,25} (Table 2). No trials demonstrated any high bias risks. All the included trials documented the randomization process. Four trials used single-blind study designs in which treatment allocation was masked from patients by sham PDT administration.^{15,17,20,25} Protocol deviation was reported in 1 trial,²⁰ but was not excessive (5 [10 %] of 50 patients), and we judged that the outcomes were unlikely to have been biased. All trials reported < 20 % of missing outcome data. No trial reported any blinding of outcome assessors. Four trials used a central reading center.^{9,15,17,20}

3.3. Primary outcomes

3.3.1. Rate of complete polyp regression

Six trials assessed the rate of complete polyp regression. Combination therapy demonstrated a significant advantage over monotherapy in studies with follow-up of ≤ 12 months (RR: 2.05, 95 % CI: 1.64–2.56); however, significance was lost with longer follow-up (RR: 1.32, 95 % CI: 0.91–1.93). Pooled analysis revealed a significantly higher rate of complete polyp regression for patients receiving combination therapy than in those receiving monotherapy (RR: 1.56, 95 % CI: 1.15–2.13, $p = 0.005$; Fig. 2).

3.3.2. Number of anti-VEGF injections

Five trials compared anti-VEGF injection frequency. A significant advantage was observed for combination therapy over monotherapy (SMD: -0.73 , 95 % CI: -1.24 to -0.22) for studies with follow-up of ≤ 12 months, but not in studies with longer follow-up (SMD: -0.47 , 95 % CI: -1.08 – 0.14). After pooling the subgroup analyses, PDT plus anti-VEGF combination therapy demonstrated a pronounced reduction in the number of anti-VEGF injections (SMD: -0.65 , 95 % CI: -0.95 to -0.35 , $p < 0.0001$; Fig. 3).

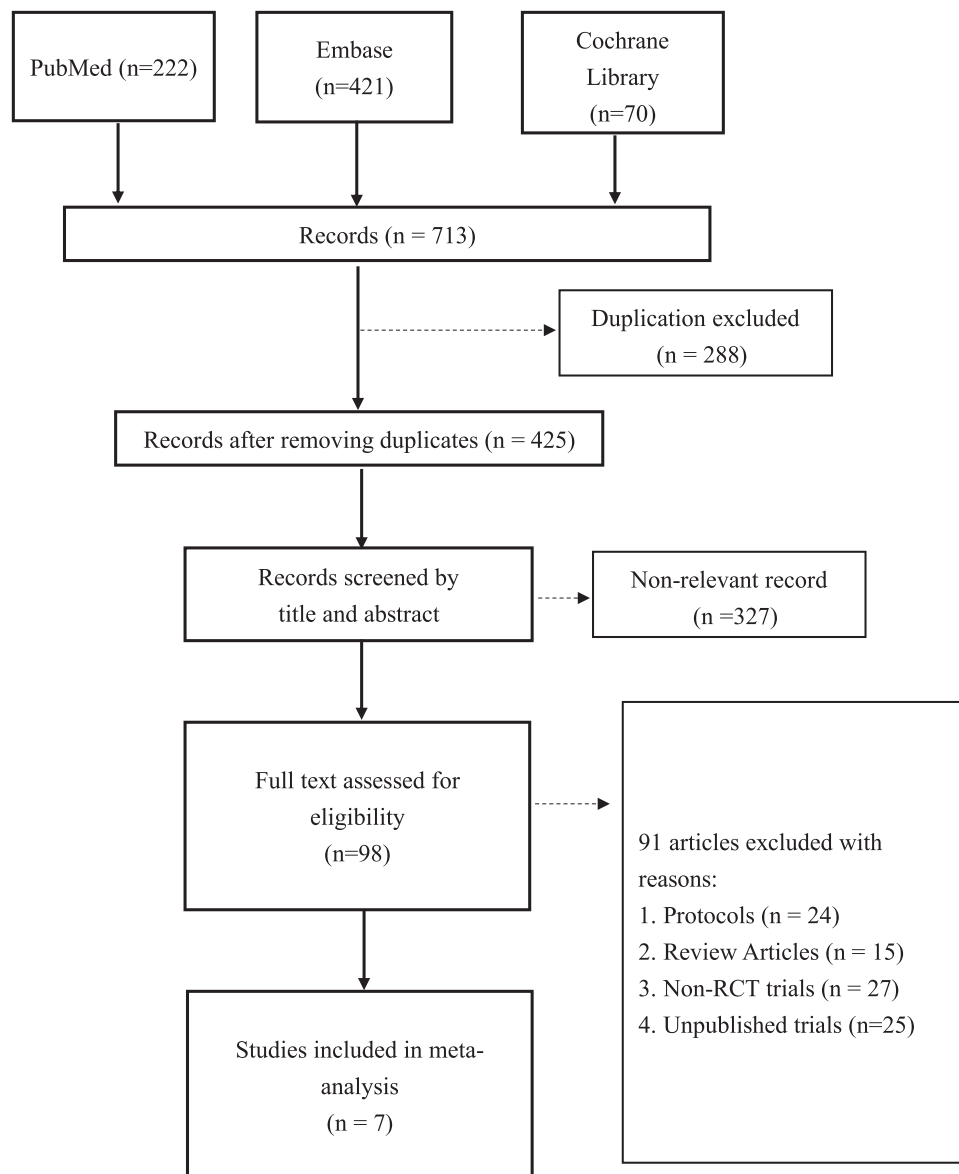


Fig. 1. Flowchart for study selection.

3.4. Secondary outcomes

3.4.1. BCVA improvement

Six trials investigated BCVA improvement. We did not observe a significant difference between combination therapy and monotherapy for studies with follow-up of ≤ 12 months (SMD: 0.73, 95 % CI: -1.22 to 2.68) or those with longer follow-up (SMD: 1.25, 95 % CI: -1.23 to 3.72). Our pooled analysis revealed a difference between combination therapy and monotherapy for BCVA improvement but with no significance (Fig. 4).

3.4.2. CRT reduction

Six trials compared CRT reduction. They revealed no significant difference between combination therapy and monotherapy for studies with follow-up of ≤ 12 months (SMD: 0.77, 95 % CI: -0.50 to 2.04) or with longer follow-up (SMD: -0.54 , 95 % CI: -2.28 to 1.20). The lack of a significant difference in CRT reduction between the combination therapy and monotherapy groups persisted when we pooled the data (SMD: 0.31, 95 % CI: -0.81 – 1.43 , $p = 0.59$; Fig. 5).

3.4.3. Rate of ocular adverse events

All 7 trials compared the rate of ocular adverse events following treatment. They revealed no significant difference between combination therapy and monotherapy, regardless of follow-up duration (≤ 12 months: RR: 1.08, 95 % CI: 0.76–1.53; >12 months: RR: 0.97, 95 % CI 0.81–1.16). Likewise, the difference remained non-significant in the pooled analysis (Fig. 6).

4. Discussion

The current systematic and meta-analytic review revealed that PDT plus anti-VEGF intravitreal combination therapy for patients with PCV resulted in better or similar outcomes to anti-VEGF monotherapy. Superior results were observed for the rate of complete polyp regression and the number of anti-VEGF injections. Therefore, PDT plus anti-VEGF intravitreal combination therapy tends to be a safe and beneficial treatment option for PCV.

PDT causes polyps regression in PCV eyes via photothrombosis, resulting in gradual pathological improvements. PDT monotherapy remains the most effective and selective means of eliminating polypoidal lesions. Positive short-term and medium-term results have been

Table 1
Characteristics of included trials.

| Author [Year] | Inclusion criteria | Number of eyes(% female) | Ethnicity | Age, year, mean ± SD | Baseline BCVA (ETDRS), mean ± SD | PDT rescue/ PRN criteria | Intervention | Follow-up Timepoints |
|---------------|---|---|---------------|------------------------------------|----------------------------------|---|---|----------------------|
| Silva 2022 | Age of ≥ 50 years; treatment-naïve PCV; ETDRS score of 25–80 and GLD of lesion of ≤ 5400 μm on FAG and ICGA | Total: 50 (50) CG: 28 (-)MG: 22 (-) | Caucasian | Total (Median & IQR): 73.5 (64–79) | Total (Median & IQR): 66 (56–70) | Evaluated at 28 and 40 weeks; ICGA performed when BVCA decreased to ≥ 5 ETDRS with macular fluid on SD-OCT; if active polyps confirmed with ICGA: apply sPDT or vPDT | Initial for total: IVA of 2 mg *3 (0, 4, and 8 weeks); then IVA of 2 mg T&E (16 weeks), plus sPDT or vPDT (6 mg/m ² ; fluence = 50 J/cm ²) if active polypsIf rescue criteria not met at 28 or 40 weeksTotal: IVA T&EIf rescue criteria met at 28 or 40 weeksCG: vPDT MG: sPDT | 52 weeks |
| Ogura 2021 | Age of ≥ 50 years; symptomatic macular PCV; ETDRS score of 73–24 (20/40–20/320 Snellen) | CG: 77 (24.7)MG: 75 (28.0) | Asian | CG: 73.4 ± 6.4MG: 72.5 ± 7.1 | CG: 59.8 ± 10.7MG: 58.3 ± 10.1 | [BCVA of ≤ 73 ETDRS] and [BCVA gain of < 5 or ≥ 5 but < 10 ETDRS (by investigator's judgment)] and [new or persistent fluid] and [active polyps] | Initial for total: IVA of 2 mg*3 (0, 4, and 8 weeks)If rescue criteria not met at 12 weeksTotal: IVA of 2 mg every 8 weeks until 52 weeksIf rescue criteria met at 12 weeks and laterCG: IVA of 2 mg every 4 weeks + vPDTMG: IVA of 2 mg every 4 weeks + sPDT | 96 weeks |
| Lim 2020 | Treatment-naïve symptomatic macular PCV; ETDRS of 78–24 (~20/32–20/320 Snellen equivalent) measured at 4 m; lesion GLD of < 5400 μm on ICGA | Total: 322 (30.1)CG: 168 (-)MG: 154 (-) | Asian | Total: 68.1 ± 8.8 | Total: 61.1 ± 13.2 | FA and ICGA: if disease activity with persistent or new polyps, repeat vPDT/ sPDT + IVR; if disease activity present without polyps on ICGA, only IVR was administered and continued on PRN basis | Initial for total: IVR of 0.5 mg*3 (0, 1, and 2 months)If rescue criteria not met at 3 monthsTotal: Monthly monitoring If rescue criteria met at 12 weeksCG: IVR of 0.5 mg + vPDT (verteporfin of 6 mg/m ² ; fluence = 50 J/cm ²)MG: IVR of 0.5 mg + sPDT | 24 months |
| Wong 2019 | Age of ≥ 50 years; symptomatic macular PCV (lesion GLD of <5400 mm); ETDRS of 73–24 (20/40–20/320 Snellen) | CG: 161 (30.4)MG: 157 (29.9) | †Mainly Asian | CG: 70.4 ± 8.0MG: 70.8 ± 8.4 | CG: 59.0 ± 11.5MG: 57.7 ± 11.3 | [BCVA of ≤ 73 ETDRS] and [BCVA gain of < 5 or ≥ 5 but < 10 ETDRS (by investigator's judgment)] and [new or persistent fluid] and [active polyps] | Initial for total: IVA of 2 mg*3 (0, 4, and 8 weeks)If rescue criteria not met at 12 weeksTotal: IVA of 2 mg every 8 weeks until 52 weeksIf rescue criteria met at 12 weeks and laterCG: IVA 2 mg every 4 | 52 weeks |

(continued on next page)

Table 1 (continued)

| Author [Year] | Inclusion criteria | Number of eyes(% female) | Ethnicity | Age, year, mean ± SD | Baseline BCVA (ETDRS), mean ± SD | PDT rescue/ PRN criteria | Intervention | Follow-up Timepoints |
|---------------|---|------------------------------|-----------|--|---|--|---|----------------------|
| Lai 2018 | Active macula-involved polypoidal lesions evidenced by ICGA; GLD of ≤ 5400 μm; follow-up of ≥ 12 months | CG: 16 (37.50)MG: 18 (33.33) | Asian | (Age of onset)CG: 61.06 ± 9.12MG: 64.67 ± 8.52 | (logMAR) CG: 0.94 ± 0.55MG: 0.96 ± 0.58 | VA loss of ≥ 0.1 logMAR (=5 letters of ETDRS with evidence of macular fluid); CFT increase of > 100 μm; PED enlargement; new macular hemorrhage; newly formed PCV; evidence of persistent fluid 1 month after previous injection | weeks + vPDTMG: IVA 2 mg every 4 weeks + sPDT CG: vPDT followed by single IVR 72 h later at baseline + additional PRN IVRMG: IVR of 0.5 mg*1 at baseline + additional PRN IVR | 12 months |
| Koh 2012 | Diagnosis of PCV; ETDRS 73–24 (–20/40–20/320 Snellen); GLD of < 5400 μm; ≥ 1 of the following: (i) BVN, (ii) pulsatile polyp, (iii) nodular appearance viewed stereoscopically, (iv) hypo-fluorescent halo (first 6 min), (v) orange subretinal nodules in stereoscopic color fundus photograph, (vi) massive submacular hemorrhage | CG: 19 (42.1)MG: 21 (28.6) | Asian | CG: 63.8 ± 8.30MG: 69.3 ± 8.27 | CG: 56.6 ± 20.9MG: 49.0 ± 18.1 | Protocol-specific re-treatment criteria | CG: vPDT of 6 mg/m ² + IVR of 0.5 mg (0 months), then IVR of 0.5 mg*2 (1 and 2 months), then PRN vPDT + IVRMG: IVR of 0.5 mg *3 (0, 1, and 2 month), then PRN IVR | 6 months |
| Lim 2012 | Age of ≥ 50 years; BCVA of ≤ 0.6 in study eye | CG: 5 (40) MG: 5 (0) | Asian | CG: 57.8 ± 7.08MG: 68.6 ± 6.41 | CG: 56 ± 19.08MG: 57 ± 10.77 | - | CG: vPDT + IVB of 1.25 mg (0 weeks), then IVB of 1.25 mg*2 (6 and 12 weeks), then PRN IVBMG: IVB of 1.25 mg *3 (0, 6, and 12 weeks), then PRN IVB | 48 weeks |

Abbreviations: BCVA: best corrected visual acuity; BVN: branching vascular network; CFT: central foveal thickness; CG: PDT plus anti-VEGF combined therapy group; ETDRS: Early Treatment Diabetic Retinopathy Study; FAG: fluorescein angiography; GLD: greatest linear dimension; ICGA: indocyanine green angiography; IVA: intravitreal aflibercept injection; IVB: Intravitreal bevacizumab injection; IVR: Intravitreal ranibizumab injection; LogMAR: logarithm of the minimum angle of resolution; MG: anti-VEGF monotherapy group; OCT: optical coherence tomography; PDT: photodynamic therapy; PRN: pro re nata; SD-OCT: spectral domain-domain optical coherence tomography; sPDT: sham PDT; T&E: treat-and-extend; vPDT: verteporfin PDT; VA: Visual acuity †296 Asian, 22 non-Asian

reported;¹⁶ however, outcomes, including visual acuity, damage to the choroidal vasculature, and retinal pigment epithelial tear or hemorrhage, become suboptimal with longer follow-up.^{2,23}

The anti-vasoproliferative and anti-permeative properties of anti-VEGF injections have proven effective in controlling nAMD;¹ however, the benefits of anti-VEGF monotherapy to treat PCV remain unclear. Improved BCVA with reduced subretinal hemorrhage has been reported,¹¹ but challenges include limited polyp regression rate,⁶ poor control over choroidal vascular changes,⁴ and persistently branching vascular networks.^{8,9} Additionally, the aqueous VEGF levels in PCV are

significantly lower than those in nAMD.²² Altogether, these reports indicate that polypoidal dilation of the PCV choroid may not depend on the actions of VEGF as much as age-related neovascularization does. Thus, the regression of polypoidal lesions should be emphasized as an important aspect of PCV treatment. Our findings support the use of PDT plus anti-VEGF combination therapy.²

PDT plus anti-VEGF injection combination therapy can create a synergistic effect that eliminates polypoidal lesions, lessens fluid leakage, suppresses inflammation, and maintains visual acuity. The EVEREST study by Koh and coworkers⁹ was the first RCT to address this

Table 2
Risk-of-bias assessment.

| Author [Year] | Bias arising from the randomization process | Bias because of deviations from intended interventions | Bias because of missing outcome data# | Bias in measurement of the outcome | Bias in selection of the reported result | Overall risk of bias |
|---------------------|---|--|---------------------------------------|------------------------------------|--|----------------------|
| Silva et al. [2022] | Low | Some concerns | Low | Low | Low | Some concerns |
| Ogura et al. [2021] | Low | Low | Low | Low | Low | Low |
| Lim et al. [2020] | Low | Low | Low | Low | Low | Low |
| Wong et al. [2019] | Low | Low | Low | Some concerns | Low | Some concerns |
| Lai et al. [2018] | Low | Low | Low | Some concerns | Low | Some concerns |
| Koh et al. [2012] | Low | Low | Low | Low | Low | Low |
| Lim et al. [2012] | Low | Low | Low | Some concerns | Low | Some concerns |

< 20 % Missing: Low; 20 %–30 % Missing: Some Concerns; > 30 % Missing: High

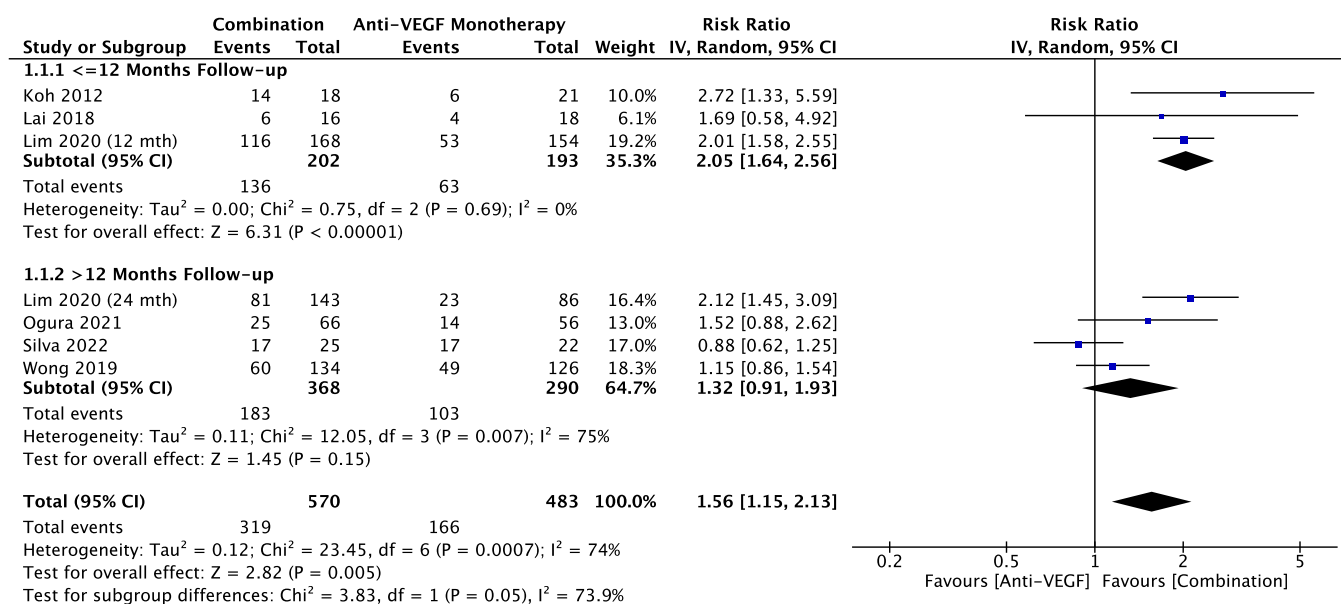


Fig. 2. Forest plot for comparison of the rates of complete polyp regression between PDT plus anti-VEGF combination therapy and anti-VEGF monotherapy.

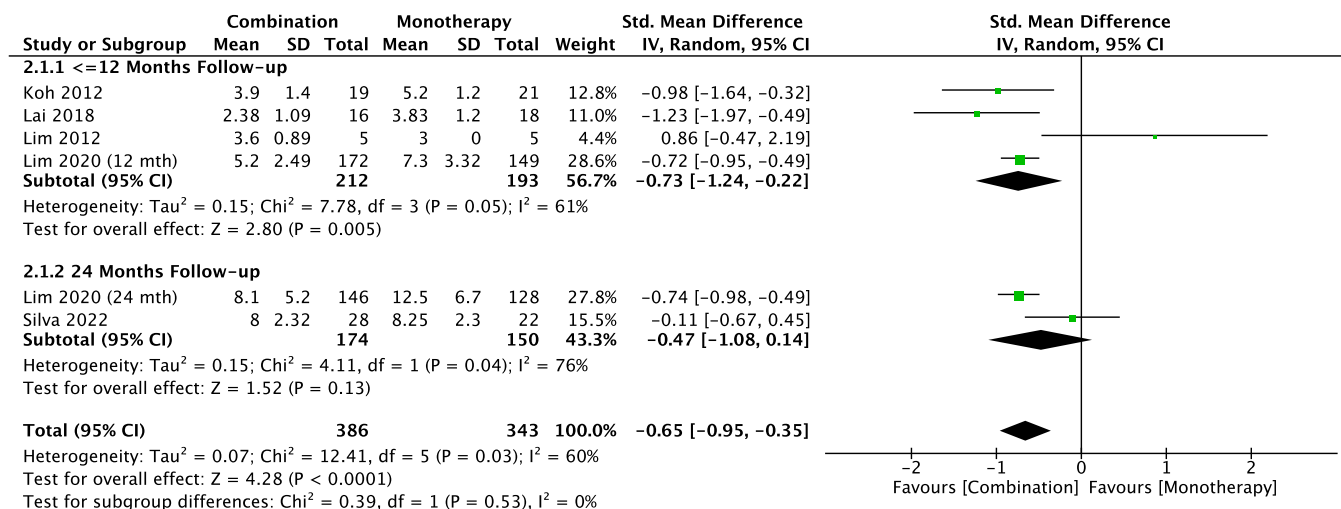


Fig. 3. Forest plot for comparison of the number of anti-VEGF injections between PDT plus anti-VEGF combination therapy and anti-VEGF monotherapy.

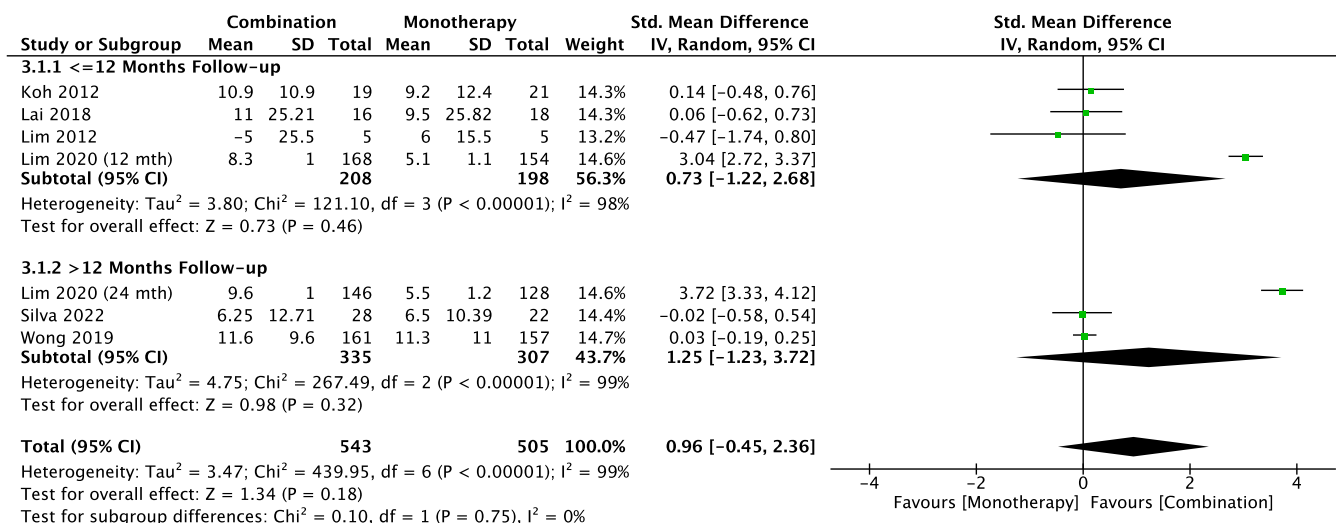


Fig. 4. Forest plot for comparison of BCVA improvement between PDT plus anti-VEGF combination therapy and anti-VEGF monotherapy.

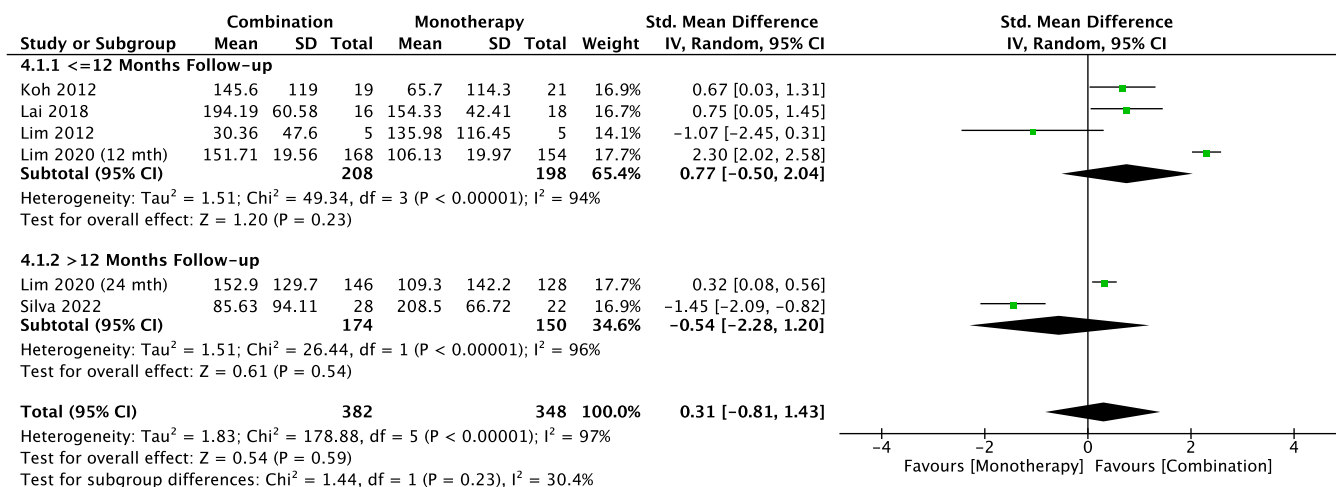


Fig. 5. Forest plot for comparison of CRT reduction between PDT plus anti-VEGF combination therapy and anti-VEGF monotherapy.

issue. The findings demonstrated that ranibizumab combined with PDT or PDT monotherapy was superior to ranibizumab monotherapy for complete polyp regression.

Previous meta-analyses have supported the use of combination therapy of PDT plus anti-VEGF injection for PCV treatment. In one review,²⁷ a systematic search of the Cochrane Library, PubMed and Embase via Ovid database system was performed to identify relevant studies up to 9 January 2017. They conducted a meta-analysis of 9 studies to compare the efficacy and safety between combined therapy and anti-VEGF monotherapy for PCV. The BCVA in combined therapy group were significantly better than those of anti-VEGF monotherapy group at 6, 24 and 36 months, with pooled weighted mean differences (WMDs) of 0.12 (0.06, 0.18), 0.25 (0.12, 0.38) and 0.28 (0.13, 0.43), respectively. The CRT reductions in combined therapy group were higher than that in anti-VEGF monotherapy group at 1, 3, 6 and 9 months, with pooled WMDs of 63.90 (20.41, 107.38), 33.47 (4.69, 62.24), 30.57 (0.12, 60.01) and 28.00 (2.51, 53.49), respectively. The regression rate of polyps in combined therapy group was much higher than that in anti-VEGF monotherapy group [risk difference: 0.47 (0.26, 0.68); P < 0.0001]. In another previous review,²⁸ the PubMed, EMBASE, and Ovid databases were searched up to January, 2020, to identify related studies. A total of 104 studies with 5816 patients was included. The general rate of complete polyp regression at 12 months post-treatment was 64 % (95 % CI [57–71 %]), with 89 % (95 % CI

[81–95 %]) for PDT monotherapy, 78 % (95 % CI [68–86 %]) for PDT with anti-VEGF, and 42 % (95 % CI [35–49 %]) for anti-VEGF alone; PDT with anti-VEGF showed the best visual improvement and the highest rate of dry macula (91 %, 95 % CI [78–99 %]). However, this review only performed meta-analysis on complete polyp regression and included RCTs and non-RCTs, thereby causing greater heterogeneity than in our review.

In contrast, our meta-analysis was exclusively performed on RCTs. These included EVEREST, PLANET²⁵ (with its updated focus on the Japanese population¹⁷), EVEREST II (with its latest update of data in 2020¹⁵), ATLANTIC²⁰ (never reviewed meta-analytically before), and other relevant studies. Therefore, it is the most up-to-date and comprehensive collection of RCTs, providing an evidence-based guideline for clinicians considering first-line management for patients with PCV.

5. Conclusion and limitations

The current study has several limitations. First, the relatively small number of study records limits the applicability of the results. Future RCTs that address the current topic are necessary to strengthen our conclusions. Second, as part of their study protocols, 4 of the 7 included trials^{15,17,20,25} applied universal anti-VEGF monotherapy for both groups before randomization. Such universal prerandomization

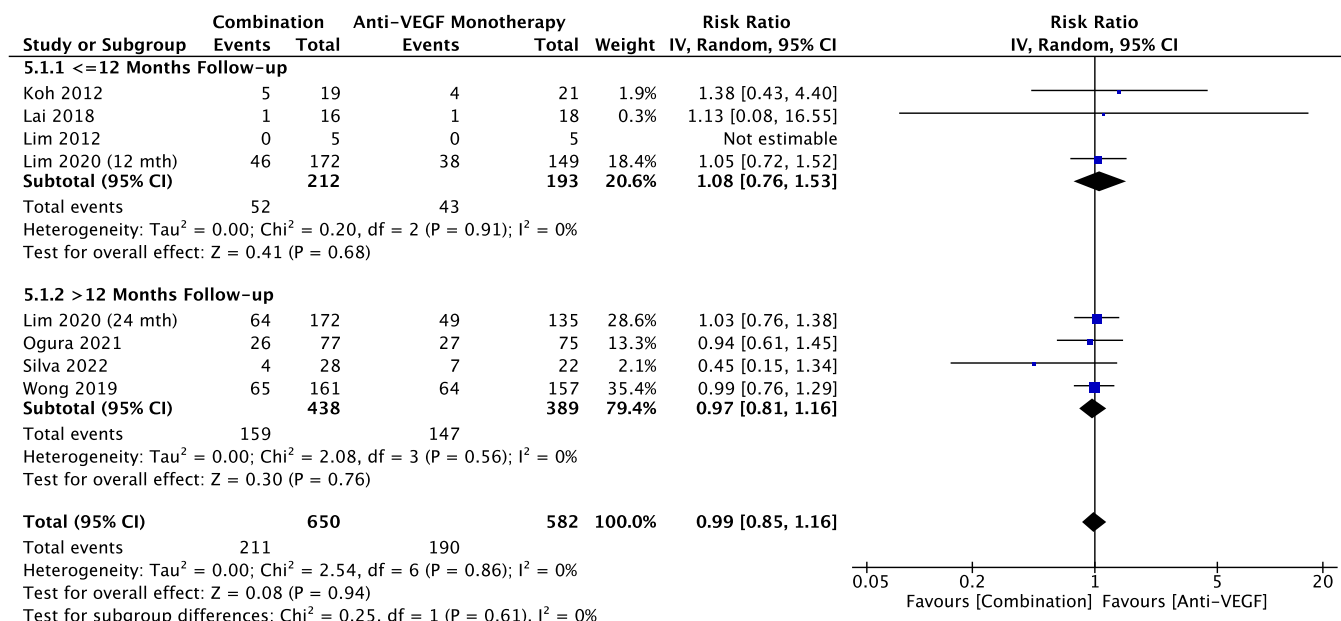


Fig. 6. Forest plot for comparison of the rate of ocular adverse events between PDT plus anti-VEGF combination therapy and anti-VEGF monotherapy.

treatment may not significantly lead to differences between the patient groups at randomization, but might give rise to heterogeneity in the calculation of follow-up timepoints. As a result, the effects of pre-randomization remain to be addressed, and further analyses are advised to focus on such effects if there are enough studies. Third, injection of different anti-VEGF may result in different effects. Due to the smaller number of our included trials, the effects of different anti-VEGF were not discussed in depth and would require elucidation through future studies. Fourth, the study populations were predominantly Asian in all studies except one.²⁰ Future RCTs that involve patients with other ethnicities are required. Finally, the sex and/or gender characteristics of the current analysis were not investigated. Addressing these limitations in future analyses will enhance the understanding of the efficacy of PDT plus anti-VEGF combination therapy.

In conclusion, the trials analyzed in this systematic review demonstrated that PDT plus anti-VEGF injection combination therapy facilitates increased rates of complete polyp regression and reduces the number of required anti-VEGF injections compared with anti-VEGF monotherapy in patients with PCV. Regarding functional and anatomical outcomes and treatment safety, combination anti-VEGF therapy performs similarly to monotherapy. Therefore, we conclude that PDT plus anti-VEGF combination therapy constitutes a safe and effective modality and should be considered as a first-line treatment for patients with PCV.

CRedit authorship contribution statement

Po-Chen Tseng: Writing – review & editing, Supervision, Conceptualization. **HY Lin:** Methodology, Data curation. **Ting-Han Lin:** Writing – original draft, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Method of literature search

Relevant studies were retrieved from PubMed, Embase, and Cochrane databases that were published from the inception of the databases to July 31st, 2024. The following search terms and medical subject headings were used in various combinations: “verteporfin,” “photodynamic therapy,” “anti-VEGF,” “ranibizumab,” “aflibercept,” “bevacizumab,” and “polypoidal choroidal vasculopathy.” Further, reference sections of retrieved studies were manually searched and known researchers with relevant expertise were contacted. The systematic review and meta-analysis demonstrated herein was accepted by the online PROSPERO International Prospective Register of Systematic Reviews of the National Institute for Health Research (CRD42023471362).

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Data availability

The data supporting the findings of the current study are publicly available in the PubMed, Embase, and Cochrane databases. These data were procured from the following resources accessible in the public domain: <https://pubmed.ncbi.nlm.nih.gov/>, <https://www.embase.com>, <https://www.cochranelibrary.com/>.

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