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Macular Atrophy in Neovascular Age-related Macular Degeneration

A Systematic Review and Meta-analysis

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Topic: Macular atrophy incidence in neovascular age-related macular degeneration (AMD) patients undergoing anti-VEGF treatment.

Clinical Relevance: Macular atrophy is a significant event that may occur in eyes with neovascular AMD treated with anti-VEGF therapy.

Methods: We conducted a systematic review and meta-analysis following PRISMA guidelines (PROSPERO, CRD42024474924). A comprehensive literature search of MEDLINE, EMBASE, and Web of Science was performed up to November 1, 2023. Randomized and nonrandomized studies of treatment-naive neovascular AMD patients reporting macular atrophy incidence at 24 ± 3 months after anti-VEGF therapy were eligible. Two independent reviewers conducted screening, data extraction, and quality assessment. For randomized controlled trials, the Cochrane Risk of Bias 2 tool was employed, whereas nonrandomized studies were evaluated using the Risk Of Bias In Nonrandomized Studies of Interventions tool. Random-effects meta-analysis models accounted for study variability. Heterogeneity was assessed with the I^2 statistic, and publication bias by funnel plots and Egger test. The primary outcome was the incidence of new macular atrophy at 24 months post-treatment, with secondary outcomes at 12 months. Atrophy was diagnosed using color fundus photograph, fluorescein angiography, fundus autofluorescence, OCT, or multimodal imaging.

Results: Twenty-three studies met the inclusion criteria for qualitative analysis, with 11 included in the meta-analysis (N = 3013 eyes). The pooled 24-month incidence of macular atrophy was 29% (95% confidence interval [CI]: 20%–38%, I^2 = 93%). Subgroup analysis revealed incidence rates of 26% (95% CI: 15%–37%, I^2 = 88%) for 814 eyes with type 1/2 macular neovascularization (MNV), 49% (95% CI: 18%–80%, I^2 = 92%) for type 3 MNV (N = 230 eyes), and 29% (95% CI: 18%–40%, I^2 = 96%) for all MNV types (N = 2131 eyes). The pooled 12-month incidence among 2214 eyes was 11% (95% CI: 4%–18%, I^2 = 93%). The certainty of evidence, as assessed by Grading of Recommendations, Assessment, Development and Evaluation, was low.

Conclusion: Although this meta-analysis has limitations, including a moderate risk of bias in nonrandomized studies, inconsistencies in the results indicated by high heterogeneity, and imprecision due to the different imaging modalities used to diagnose macular atrophy, our results suggest that macular atrophy could be a common complication in patients with neovascular AMD receiving anti-VEGF therapy.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Retina 2025;9:625-644 © 2025 by the American Academy of Ophthalmology.*

Supplemental material available at www.ophthalmologyretina.org.

Neovascular exudative age-related macular degeneration (AMD) is a significant cause of vision impairment among individuals aged ≥50 years.[1,2] In patients with AMD, the emergence of macular neovascularization (MNV) and consequent exudation can reduce visual acuity.[3] Neovessels complicating AMD may originate from either the choroid (type 1 and type 2) or the retina (type 3).[2]

Despite notable advancements in visual outcomes among patients with exudative neovascular AMD attributed to the effectiveness of anti-VEGF therapy in resolving exudation,[4] there are potential macular complications that may emerge in this context.[5] These include the development of macular atrophy, which can occur and profoundly impact clinical outcomes in patients with neovascular AMD.[6–14] Importantly, it has been suggested to use the term "macular atrophy" to characterize areas of retinal pigment epithelium (RPE) atrophy and photoreceptor loss, regardless of whether this complication is associated with MNV or not. In contrast, the term "geographic atrophy" typically refers to cases lacking any concurrent exudative MNV.[15] It is important to highlight that, although there is a semantic distinction between geographic atrophy and macular

https://doi.org/10.1016/j.oret.2025.01.011
ISSN 2468-6530/25

atrophy based on the absence or presence of MNV, the development of macular atrophy in exudative MNV is a complex process. It is not solely attributed to neovessels and exudation, as several factors are involved, including those typically associated with dry AMD, such as drusen-related RPE atrophy.[16,17]

Existing reviews on the subject are primarily qualitative analyses within broader review topics,[2,18,19] and there have not been any published systematic reviews and meta-analyses specifically exploring the incidence of new macular atrophy in patients with exudative neovascular AMD. Our research aimed to address this gap by answering the following question: in treatment-naïve exudative neovascular AMD eyes without evidence of macular atrophy at baseline, what is the incidence of macular atrophy within the initial 24 months of anti-VEGF treatment? Importantly, we also aimed to categorize this incidence according to the type of MNV affecting patients with AMD. By exploring these associations, we aimed to further uncover mechanisms of neovascular AMD and provide useful information for clinical advice and guideline development.

Methods

Review Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[20] This study adhered to the Declaration of Helsinki. The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024474924). This study is a systematic review and meta-analysis that does not involve human subjects, and did not require IRB approval. Individual patient-level consent was not required.

Eligibility Criteria and Outcomes

A population, intervention, comparator, outcome, study design framework was used to determine study eligibility (Fig 1). (P): Patients diagnosed with treatment-naïve neovascular exudative AMD in $\geq$1 eye, with no evidence of macular atrophy at baseline and followed for at least 24 months. The diagnosis was confirmed through $\geq$1 of the following: color fundus photography (CFP), fluorescein angiography (FA), indocyanine green angiography, OCT, or OCT angiography. All types of MNVs were considered. (I): Patients treated with any available anti-VEGF drugs under any regimen. (C): None. (O): The primary outcome was the rate of new macular atrophy development 24 months after initiating anti-VEGF treatment in patients with no baseline macular atrophy. Studies that only reported the overall incidence of macular atrophy without providing specific incidence rates for eyes that were atrophy-free at baseline were excluded. Only studies reporting data either exactly after 24 months of follow-up or a mean follow-up of 24 $\pm$ 3 months were included. Macular atrophy was defined as atrophy either within, adjacent, or nonadjacent to the MNV lesion and was assessed using established diagnostic techniques such as CFP, FA, fundus autofluorescence (FAF), near-infrared reflectance, OCT, or a multimodal approach. Secondary outcomes included the 24-month atrophy incidence based on the MNV type at baseline and the 12-month incidence of macular atrophy. (S): Eligible studies were longitudinal, retrospective or prospective, randomized, or nonrandomized.

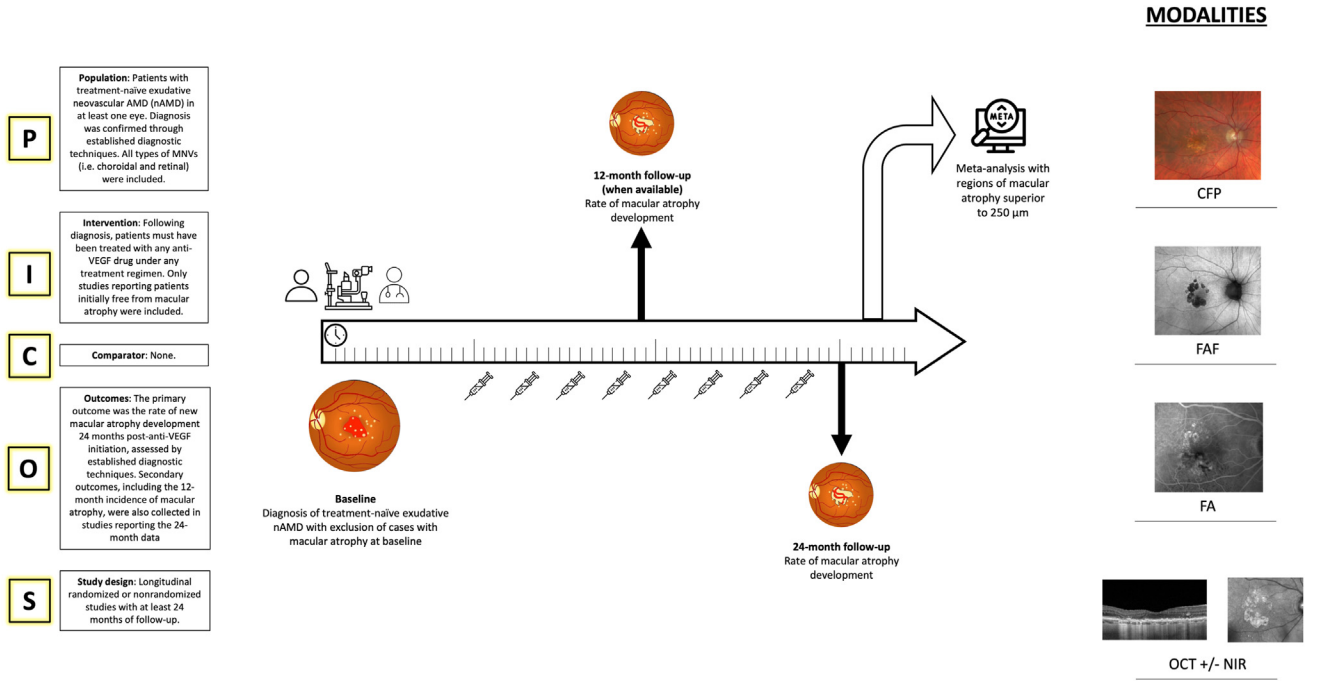

Figure 1. Graphical overview of the patient (P), intervention (I), comparison (C), outcomes (O), and study design (S) framework of the systematic review. We selected studies including patients with treatment-naïve exudative neovascular age-related macular degeneration with no baseline macular atrophy (left side of the picture). After diagnosis, patients must have been treated with any anti-VEGF drug under any treatment regimen (central side of the picture). The primary outcome was the incidence of new macular atrophy after 2 years of treatment, diagnosed using established techniques such as color fundus photograph (CFP), fluorescein angiography (FA), fundus autofluorescence (FAF), near-infrared reflectance (NIR), OCT, or a multimodal approach (right side of the picture).

Search Strategy

A comprehensive literature search was conducted across MEDLINE (via PubMed), EMBASE, and Web of Science for English-language studies without time constraints. The search combined MeSH terms and free text terms to capture all relevant studies. The detailed search strategies are available in Table S1 (available at www.ophthalmologyretina.org). The most recent search was completed on November 1, 2023. Bibliographies of included studies and relevant review articles were hand-searched by 2 independent reviewers for additional sources. Two reviewers (A.B. and A.C.) independently conducted the search to reduce bias.

Study Selection, Data Collection, and Risk of Bias Assessment

Study selection was performed using Covidence,[21] which automatically removed duplicates. Two reviewers (A.B. and A.C.) independently screened the titles and abstracts against inclusion and exclusion criteria. Full-text articles were retrieved for detailed assessment, with discrepancies resolved by consensus. A standardized form was used for both phases of study selection.

The 2 authors independently extracted data to minimize bias. The data were recorded on a prespecified spreadsheet and included study design, patient demographics, imaging modalities used, criteria for diagnosis of neovascular AMD and macular atrophy, type of anti-VEGF drug administered, treatment protocols, and outcome measures.

The quality of the included studies was assessed using appropriate risk of bias tools. For randomized controlled trials (RCTs), the Cochrane Risk of Bias 2 tool[22] was used to evaluate the risk of bias across 5 domains, whereas for nonrandomized studies, the 7-domain Risk Of Bias In Non-randomized Studies of Interventions tool was used.[23] These assessments were conducted independently by 2 authors, with discrepancies resolved through discussion and consensus.

We performed a Grading of Recommendations, Assessment, Development and Evaluation assessment to evaluate the overall certainty of evidence for the incidence of macular atrophy outcomes, considering factors such as risk of bias, inconsistency, indirectness, imprecision, and potential publication bias.

Qualitative and Quantitative Analyses

Data were synthesized and presented qualitatively in text and tables. Studies that reported the incidence of new macular atrophy after 2 years of anti-VEGF therapy and used a minimum atrophy size criterion of at least 0 μm in diameter or greatest linear dimension were included in the meta-analysis. For the primary outcome, the incidence of new macular atrophy 24 months after anti-VEGF therapy, quantitative analysis was performed using random-effects meta-analysis models to account for within- and between-study variability. These models also analyzed the 12-month incidence of macular atrophy. Subgroup analyses were conducted based on the type of MNV (type 1/2, type 3, and studies including all MNV types). Eyes with polypoidal choroidal vasculopathy were included in the type 1 MNV group, consistent with the classification proposed by Spaide et al.[24] Heterogeneity was assessed using the I^2 statistic, with significant heterogeneity considered if $I^2 > 50\%$.

Potential publication bias was evaluated through visual inspection of funnel plots and Egger test. Sensitivity analysis was performed to assess the robustness of the results by systematically omitting each study and recalculating the pooled estimates.

For each meta-analytic calculation, we reported point estimates and 95% confidence interval (CI) to assess statistical significance. All statistical analyses were performed using RStudio (version 2024.04.1)[25,26] and the "meta" package (version 7.0.0).[27]

Results

Study Selection

The search identified 3872 records after duplicate removal. After title and abstract screening, 3573 records were excluded, leaving 299 records for full-text eligibility assessment. Of these, 23 studies met all eligibility criteria and were included in the qualitative analysis. Additionally, 11 studies, each with unique cohorts meeting the size criterion (≥250 μm) for macular atrophy diagnosis, were included in the quantitative analysis. The study selection process is detailed in Figure S2 (available at www.ophthalmologyretina.org).

Study Characteristics

The qualitative synthesis included 23 studies published between 2014 and 2023, encompassing 18 unique cohorts.[8,9,28–48] Geographically, these cohorts included 6 from Asian centers,[29,31,33,41,43,45] 5 from North America,[8,28,30,32,34–36,39,48,49] 4 from Europe,[8,37,38,44] 1 from Australia,[40] and 2 multicentric cohorts from the United States, Europe, and Australia.[42,46] Eight reports originated from single-center studies,[29,31–33,37–39,45] whereas 15 were multicentric.[8,9,28,30,34–36,40–44,46–48]

The study designs included 10 retrospective observational studies,[29,31–33,39,41,42,44–46] 3 prospective nonrandomized cohorts,[37,38,43] and 10 RCTs.[8,9,28,30,34–36,40,47,48] Among the RCTs, 4 were post hoc analyses from A Study of Ranibizumab Administered Monthly or on an As-needed Basis in Patients With Subfoveal Neovascular Age-related Macular Degeneration (HARBOR) trial cohort,[9,15,34,36,48] 3 reported data from the Comparisons of Age-Related Macular Degeneration Treatments Trials (CATT) trial,[15,28,30,35] and 1 each from A Comparison of Ranibizumab and Aflibercept for the Development of Geographic Atrophy in (Wet) AMD Patients (RIVAL),[40] Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN),[8] and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) trials.[47]

The included studies collectively reported on a total of 5246 unique eyes from 5175 patients with treatment-naïve neovascular AMD. Out of these, 4433 (84.5%) eyes showed no signs of macular atrophy at baseline and completed 2 years of follow-up.

The mean age of patients at baseline ranged from 69.5[43] to 86.7[32] years.

Diagnostic methods for neovascular exudative AMD included angiographic modalities (FA, indocyanine green angiography, OCT angiography, or combinations thereof) in 21 studies, whereas 2 studies used only structural spectral-domain OCT (SD-OCT),[32,39] therefore not distinguishing between MNV types. Regarding MNV classification, 5 studies specifically focused on choroidal (type 1, type 2, or mixed type 1/2) MNVs,[41,43,45–47] 3 on retinal (type 3) MNVs,[29,31,33] and 15 on both choroidal and retinal MNVs.[8,9,28,30,32,34–40,42,44,48] Detailed characteristics of the included studies and baseline patient demographics are summarized in Table 2.

Table 2. Study Characteristics and Baseline Patient Demographics

Study	Study Design	Centers; Country	Total Eyes (n), Patients (n) at Baseline	Male, %	Patient Age (yrs) Mean ± SD or Mean (Range)	Imaging Modality for Baseline nAMD Diagnosis	Type of MNV	Eyes with No Macular Atrophy at Baseline
Abdelfattah et al[32]	Retrospective; observational	Single center; Unites States	54; 46	45.70%	86.7 ± 6.8	SD-OCT	Any	29 (53.7%)
Baek et al[31]	Retrospective; observational	Single center; South Korea	91; 74	21.60%	74.2 ± 6.4	CFP, SD-OCT, FA, and ICGA	Type 3 (100%)	91 (100%)
Bailey et al[8]	Prospective; RCT (IVAN)	Multicentric; United Kingdom	596; 596	40.40%	77.5 ± 7.5	CFP, FA, and TD/SD-OCT	Any	520 (87.2%)
Blazaki et al[44]	Retrospective; observational	Multicentric; Greece	53; 53	43.40%	81.36 ± 7.91	FA	Type 1 (83%); type 2 (11%); type 3 (6%)	53 (100%)
Blodi et al[47]	Prospective; RCT (MARINA)	Multicentric; Unites States	473; 473	NR	NR	CFP and FA	Type 1 or mixed type 1 and 2	418 (88.4%)
Cho et al[29]	Retrospective; observational	Single center; South Korea	43; 38	47.40%	74.8 ± 7.1	SD-OCT, FA, and ICGA	Type 3 (100%)	43 (100%)
Cho et al[33]	Retrospective; observational	Single center; South Korea	38; 38	52.60%	74.3 ± 7.5	CFP, SD-OCT, FA, and ICGA	Type 3 (100%)	38 (100%)
Cho et al[45]	Retrospective; observational	Single center; South Korea	509; 509	54%	70.1 ± 8.5	SD-OCT, FA, and ICGA	Type 1 (50.9%); PCV (37%); type 2 (12.1%)	509 (100%)
Corvi et al[46]	Retrospective; observational	Multicentric; Italy, Unites States	44; 44	33%	77.9 ± 6.9	SD-OCT, FA, and ICGA	Type 1 (100%)	44 (100%)
Eng et al[39]	Retrospective; observational	Single center; Unites States	197; 158	37.10%	78.9 ± 14.6	SD-OCT	Any	82 (41.6%)
Gillies et al[40]	Prospective; RCT (RIVAL)	Multicentric, Australia	281; 281	47.30%	77.63 ± 8.0	SD-OCT and FA	Any	260 (92.5%)
Grunwald et al[28]	Prospective; RCT (CATT)	Multicentric; Unites States	1185; 1185	38.20%	79.2 ± 7.0	CFP, FA, and TD/SD-OCT	Any	1024 (86.4%)
Grunwald et al[30]	Prospective; RCT (CATT)	Multicentric; Unites States	1185; 1185	38.20%	79.2 ± 7.0	CFP, FA, and TD/SD-OCT	Any	1099 (92.7%)
Grunwald et al[35]	Prospective; RCT (CATT)	Multicentric; Unites States	1185; 1185	38.20%	79.2 ± 7.0	CFP, FA, and TD/SD-OCT	Any	1102 (93.0%)
Gune et al[9]	Prospective; RCT (HARBOR)	Multicentric; Unites States	941; 941	40.70%	78.2 ± 8.24	CFP, FA, and SD-OCT	Any	761 (80.9%)
Koizumi et al[41]	Retrospective; observational	Multicentric; Japan	94; 92	75%	74.6 ± 8.3	SD-OCT, FA, and ICGA	Type 1 or 2 (41.4%); PCV (58.5%)	84 (89.4%)
Mantel et al[37]	Prospective; interventional (nonrandomized)	Single center; Switzerland	149; 149	34%	79.0 ± 7.3	FA and ICGA	Type 1 or 2 (85.2%); type 3 (14.8%)	149 (100%)
Sadda et al[36]	Prospective; RCT (HARBOR)	Multicentric; Unites States	1095; 1095	41%	78.7 ± 8.3	CFP, FA, and OCT	Any	972 (88.8%)
Sarraf et al[34]	Prospective; RCT (HARBOR)	Multicentric; Unites States	1097; 1097	41%	78.7 ± 8.3	CFP, FA, and OCT	Any	NR
Sato et al[43]	Prospective; observational	Multicentric; Japan	28; 28	75%	69.5 (43–85)	CFP, SD-OCT, FA, and ICGA	Type 1 (17.9%); type 2 (17.9%); PCV (64.3%)	28 (100%)
Sitnilska et al[38]	Prospective; interventional (nonrandomized)	Single center; Germany	52; 52	52%	76.01 ± 7.1	CFP, FAF, NIR, SD-OCT, FA, and ICGA	NA	52 (100%)

Table 2. (Continued.)

Study	Study Design	Centers; Country	Total Eyes (n), Patients (n) at Baseline	Male, %	Patient Age (yrs) Mean ± SD or Mean (Range)	Imaging Modality for Baseline nAMD Diagnosis	Type of MNV	Eyes with No Macular Atrophy at Baseline
Spooner et al[42]	Retrospective; observational	Multicentric; Australia and Italy	264; 264	44%	77.5 ± 8.5	SD-OCT and FA	Any	205 (77.6%)
Staurenghi et al[48]	Prospective; RCT (HARBOR)	Multicentric; Unites States	922; 922	NR	NR	CFP, FA, and OCT	Any	593 (64.3%)

CFP = color fundus photography; CATT = Comparisons of Age-Related Macular Degeneration Treatments Trials; FA = fluorescein angiography; FAF = fundus autofluorescence; HARBOR = A Study of Ranibizumab Administered Monthly or on an As-needed Basis in Patients With Subfoveal Neovascular Age-related Macular Degeneration; ICGA = indocyanine green angiography; IVAN = Inhibition of VEGF in Age-related choroidal Neovascularisation; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; NA = not applicable; nAMD = neovascular age-related macular degeneration; NIR = near-infrared reflectance; NR = not reported; PCV = polypoidal choroidal vasculopathy; RCT = randomized controlled trial; RIVAL = A Comparison of Ranibizumab and Aflibercept for the Development of Geographic Atrophy in (Wet) AMD Patients; SD = spectral-domain; TD = time-domain.

All included eyes received either aflibercept (2 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 or 0.5 mg). Most nonrandomized studies allowed flexibility in drug choice based on patient response. However, one study exclusively used aflibercept,[41] and another exclusively administered ranibizumab.[29] In RCTs, patients were assigned to different treatment arms with no possibility of drug reassignment.

For diagnosing macular atrophy, 6 studies used only SD-OCT B-scans,[9,32,39,44,46,48] 5 of which identified complete RPE and outer retinal atrophy lesions.[9,39,44,46,48] However, 2 of these latter studies included patients from the HARBOR trial, which used a minimum size criterion of ≥125 μm instead of ≥250 μm because the protocol was finalized before the Classification of Atrophy Meetings criteria publication.[9,48,49] Six studies identified macular atrophy as regions indicative of atrophy using multiple imaging modalities (CFP, FA, FAF, and near-infrared reflectance) and confirmed RPE atrophy presence on SD-OCT B-scans.[29,31,33,37,42,45] Seven studies relied exclusively on CFP or FA for atrophy assessment, [28,30,34–36,43,47] whereas 3 alternatively used different imaging modalities (CFP, FA, FAF, or OCT),[8,38,40] and 1 used FAF only.[41]

Notably, 14 studies defined atrophic lesions as having a minimum size of 250 μm in diameter (on OCT B-scans) or the greatest linear dimension (on en face modalities), with 11 of these (unique cohorts) included in the meta-analysis.

Details on treatment protocols and macular atrophy diagnosis criteria are summarized in Table 3.

Results of Individual Studies

Qualitative Analysis. Table 3 reports the 12- and 24-month macular atrophy outcomes. The overall rate of new macular atrophy development after 24 months of anti-VEGF therapy ranged from 14.4%[30] to 53.7%.[39] In studies using only SD-OCT for atrophy diagnosis, the 2-year incidence ranged from 18.9% to 53.7%,[39] whereas studies using CFP or FA reported rates from 14.4%[30] to 38.6%.[47] Studies employing a combination of both en face and B-scan images showed an incidence ranging from 14.9%[45] to 42.3%.[37] Fourteen studies reported the incidence of macular atrophy after 12 months of follow-up, with rates ranging from 1.9%[44] to 28.8%.[38]

In nonrandomized settings, the incidence of new macular atrophy at 2 years ranged from 14.9%[45] to 53.7%,[39] whereas in RCTs it ranged from 14.4%[30] to 38.6%.[47] Among studies reporting on the HARBOR cohort, 2 reported 2-year new atrophy incidence diagnosed with CFP or FA, with rates of 29.4%[36] and 30.7%,[34] whereas 2 studies diagnosed complete RPE and outer retinal atrophy lesions (≥125 μm) on SD-OCT, with rates of 32.3%[9] and 32.9%.[48] In the CATT trial, post hoc analyses reassessed atrophy grading on CFP or FA over time, with 2-year new atrophy rates ranging from 14.4%[30] to 18.3%.[28] In the RIVAL,[40] IVAN,[8] and MARINA[47] post hoc analyses, 2-year atrophy rates were 34.7%, 25%, and 38.6%, respectively. Additionally, Blodi et al[47] compared the 2-year atrophy incidence in eyes treated with ranibizumab (0.3 or 0.5 mg) compared with sham injections, with incidences of 38.6% versus 21%, respectively.

Meta-Analysis. The meta-analysis included 11 studies (3013 eyes initially free from atrophy) assessing the incidence of new macular atrophy after 2 years from the start of anti-VEGF therapy, using a minimum size criterion for atrophy diagnosis of at least 250

μm in diameter or in greatest linear dimension.[29,33,35–37,39,41,43–46] The pooled incidence rate was 29% (95% CI: 20%–38%), with high heterogeneity (I^2 = 93%) (Fig 3A). Sensitivity analysis confirmed the robustness of this finding, with incidence rates ranging from 26% to 31% when individual studies were omitted (Fig S4, available at www.ophthalmologyretina.org).

Subgroup analysis showed varying incidence rates according to MNV types: 26% (95% CI: 15%–37%) for type 1/2 MNV (814 eyes), 49% (95% CI: 18%–80%) for type 3 MNV (230 eyes), and 29% (95% CI: 18%–40%) for any type of MNV (2209 eyes) (Fig 5). However, no significant differences were found among subgroups (P = 0.38). Only 2 studies reported the 2-year incidence of macular atrophy among eyes with polypoidal choroidal vasculopathy, both indicating an incidence of approximately 16%.[41,43] Because of the limited number of studies providing this data, a meta-analysis for this specific subgroup is not feasible. These studies were included in the broader type 1/2 MNV group.

Among 11 studies reporting 2-year incidence data, 6 studies (2201 eyes) also reported data on the 1-year incidence,[29,33,35,36,41,44] resulting in a pooled incidence rate of 11% (95% CI: 4%–18%) (Fig 3B). The 2-year incidence of macular atrophy in this subgroup of studies, which also provided 12-month data, was 24% (95% CI: 15%–32%).

Risk of Bias, Publication Bias, and Grading of Recommendations, Assessment, Development, and Evaluation Assessment. For the RCTs in this review, most showed a low risk of bias in randomization and result selection, with some concerns about deviations from interventions, missing data, and outcome measurement (Fig S6, available at www.ophthalmologyretina.org). Nonrandomized studies, assessed with the Risk Of Bias In Nonrandomized Studies of Interventions tool, showed moderate bias, especially in confounding, participant selection, and intervention classification (Fig S7, available at www.ophthalmologyretina.org).

Publication bias was evaluated using a funnel plot (Fig S8, available at www.ophthalmologyretina.org). The observed asymmetry suggested potential bias, favoring smaller studies with higher macular atrophy rates. However, Egger test for funnel plot asymmetry was not significant (z = 1.46, P = 0.14), indicating no strong statistical evidence of publication bias.

The Grading of Recommendations, Assessment, Development, and Evaluations assessment for this review determined that the certainty of evidence regarding the incidence of macular atrophy after anti-VEGF treatment was low. This was primarily due to moderate risk of bias in nonrandomized studies, inconsistencies across findings reflected by high heterogeneity, and imprecision from varying imaging modalities employed for the diagnosis of macular atrophy. Additionally, the presence of potential publication bias, although not statistically significant, contributed to a lower overall certainty rating.

Discussion

This study systematically reviews the existing evidence regarding the occurrence of macular atrophy in patients with treatment-naïve exudative neovascular AMD without evidence of macular atrophy at baseline and who are treated with anti-VEGF therapy for a period of 2 years. Additionally, it presents separate incidence rates for both 12- and 24-month periods and stratified incidence across different types of MNV. Although numerous identified studies provided quantitative estimates for the incidence of new macular atrophy, few were specifically designed to explore the incidence and classification of MNV types. Consequently, there is considerable heterogeneity in the current evidence base, and most results are limited to a simple binary comparison (presence vs. absence), without further interrogation or sensitivity analyses. This variability has implications for directly comparing studies and conducting meta-analyses. Although efforts were made to address these limitations in the analysis, any aggregated numerical estimates should be interpreted with caution in light of the generally uncertain data quality of the included studies.

In exudative neovascular AMD, 12 months after starting anti-VEGF treatment with ranibizumab in either the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration (ANCHOR) or MARINA trials, approximately 95% of patients experienced a decline of <15 letters, whereas around 30% showed an improvement of ≥15 letters.[50,51] These outcomes remained consistent at the 24-month follow-up visit.[51,52] These initial findings marked a pivotal moment in the treatment of neovascular exudative AMD, as they demonstrated the effectiveness of anti-VEGF therapy. Macular atrophy may hinder functional improvements or cause a decline in visual acuity and reading ability despite successful treatment resulting in resolved exudation.[6–12]

Given that macular atrophy represents a common and significant risk to vision in neovascular AMD, substantial efforts have been made to determine its occurrence in these individuals. Sadda et al[36] conducted a retrospective analysis of a phase III multicenter, prospective, randomized, double-masked clinical trial assessing the effectiveness of ranibizumab for neovascular AMD (i.e., HARBOR), aiming to examine the incidence of macular atrophy within 24 months after the initiation of treatment. In the latter study, by month 12 and 24, 21.1% and 29.4% of eyes without baseline atrophy exhibited detectable macular atrophy, respectively. In an important phase IV randomized, partially masked study, Gillies et al[40] investigated differences in the development of macular atrophy over 24 months between treat-and-extend regimens of ranibizumab and aflibercept in patients with neovascular AMD. In the latter study, the percentage of patients with macular atrophy rose from 7% to 37% for those receiving ranibizumab and from 6% to 32% for those receiving aflibercept from baseline to month 24. Therefore, the above-mentioned studies indicated that approximately 1 in 3 patients with neovascular AMD develop macular atrophy within 2 years in a clinical trial setting.

We conducted a systematic review and meta-analysis that evaluated the occurrence of macular atrophy in treatment-naïve eyes with exudative neovascular AMD, who initially did not show signs of macular atrophy at baseline, and who underwent anti-VEGF therapy for a duration of 2 years. Our findings revealed an incidence rate of approximately 11% at 12 months and 29% at 24 months, which closely aligns with the values observed in a clinical trial environment.[36,40] Said

Table 3. Anti-VEGF Treatment Regimens, Imaging Modalities, Criteria for Macular Atrophy Diagnosis, and Macular Atrophy Incidence Rates at 1 and 2 Years

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Abdelfattah et al[32]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg, aflibercept 2 mg	TREX with initial loading dose	Yes	SD-OCT	At least 2 of the following: – Thinning of the RPE band, especially with an abrupt/sharp step-down in thickness – Loss of the overlying ellipsoid zone and external limiting membrane with thinning of the outer nuclear layer – Increased signal transmission into the choroid No minimum size criteria	5/29; 17.2%	8/29; 27.6%
Baek et al[31]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg	PRN without initial loading dose	Yes	NIR and SD-OCT	A high signal area on NIR and characteristics such as: – Variable shape – Sharply demarcated border – Visibility of underlying choroidal vessels with a punched-out appearance AND – Atrophic RPE layer on corresponding OCT scans No minimum size criteria	8/73; 11%	29/73; 39.7%

(*Continued*)

Table 3. (Continued.)

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Bailey et al[8]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg	PRN with initial loading dose or monthly	No	CFP, FA, or TD/SD-OCT	CFP: an area of pallor with 2 of the following: – Clearly defined margins – Scalloped margins – Identifiable large choroidal vessels FA: area of hyperfluorescence that persisted throughout the run with identifiable large choroidal vessels OCT: increased transmission of the light signal into the choroid and thinning or absence of the outer retinal layers Minimum size criteria: greatest linear dimension ≥ 175 μm	NR	130/520; 25%
Blazaki et al[44]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg, aflibercept 2 mg	PRN or TREX with initial loading dose	Yes	SD-OCT	cRORA on OCT B-scans: – Increased signal transmission through the choroid (choroidal hypertransmission) – Attenuation of the RPE band – Collapse or thinning of the outer retinal layers Minimum size criteria: greatest linear dimension ≥ 250 μm	1/53; 1.9%	10/53; 18.9%
Blodi et al[47]	Ranibizumab 0.3 or 0.5 mg	Monthly	No	CFP or FA	An area of pallor or hyperfluorescence with at least 2 of the following: – Circular shape – Sharp, well-demarcated edges – Partial or complete loss of the RPE, typically with exposure of underlying choroidal blood vessels Minimum size criteria: area ≥ 0.15 mm^2	80/316; 25.3%	122/316; 38.6%

Table 3. (Continued.)

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Cho et al[29]	Ranibizumab 0.5 mg	PRN with initial loading phase	NA	CFP/FA and SD-OCT	An area of hypopigmentation or hyperfluorescence with at least 2 of the 3 following characteristics: — Circular shape — Secondary outcomes included the 24-month atrophy incidence based on the MNV type at baseline and the 12-month incidence of macular atrophy — Visibility of underlying choroidal vessels with an "excavated or punched-out" appearance AND SD-OCT findings of increased signal transmission in the choroid and atrophic changes to the RPE Minimum size criteria: greatest linear dimension ≥ 250 μm	4/43; 9.3%	16/43; 37.2%
Cho et al[33]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg	PRN with initial loading phase	Yes	CFP/FA and SD-OCT	An area of hypopigmentation or hyperfluorescence with at least 2 of the 3 following characteristics: — Circular shape — Secondary outcomes included the 24-month atrophy incidence based on the MNV type at baseline and the 12-month incidence of macular atrophy. — Visibility of underlying choroidal vessels with an "excavated or punched-out" appearance AND SD-OCT findings of increased signal transmission in the choroid and atrophic changes to the RPE Minimum size criteria: greatest linear dimension ≥ 250 μm	3/38; 7.9%	11/38; 28.9%

(*Continued*)

Table 3. (Continued.)

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Cho et al[45]	Ranibizumab 0.5 mg, aflibercept 2 mg	PRN or TREX with initial loading dose	Yes	CFP/FAF/NIR and SD-OCT	An area of hypopigmentation or hyperfluorescence with at least 2 of the 3 following characteristics: – Circular shape – Secondary outcomes included the 24-month atrophy incidence based on the MNV type at baseline and the 12-month incidence of macular atrophy. – Visibility of underlying choroidal vessels with an "excavated or punched-out" appearance AND SD-OCT findings of increased signal transmission in the choroid and atrophic changes to the RPE Minimum size criteria: greatest linear dimension ≥ 250 μm	NR	76/509; 14.9%
Corvi et al[46]	NR	NR	NR	SD-OCT	cRORA on OCT B-scans: – Increased signal transmission through the choroid (choroidal hypertransmission) – Attenuation of the RPE band – Collapse or thinning of the outer retinal layers Minimum size criteria: diameter ≥ 250 μm	NR	20/44; 45.5%
Eng et al[39]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg, aflibercept 2 mg	TREX with initial loading dose	Yes	SD-OCT	cRORA on OCT B-scans: – Increased signal transmission through the choroid (choroidal hypertransmission) – Attenuation of the RPE band – Collapse or thinning of the outer retinal layers Minimum size criteria: diameter ≥ 250 μm	NR	44/82; 53.7%

Table 3. (Continued.)

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Gillies et al[40]	Ranibizumab 0.5 mg, aflibercept 2.0 mg	TREX with initial loading dose	No	CFP, FAF, FA, and SD-OCT	– CFP: sharply demarcated area of partial or complete depigmentation with visible underlying large choroidal vessels – FAF: an area of well-demarcated hypoautofluorescence – FA: well-demarcated areas of window defects with sharply delineated hyperautofluorescence in the late phase – SD-OCT: loss of the RPE, ellipsoid zone, and external limiting membrane with concomitant subsiding of the outer retinal layers together with increased signal transmission below Bruch membrane	62/248; 25.0%	78/225; 34.7%
Grunwald et al[28]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg	PRN or monthly	Yes	CFP or FA	Minimum size criteria: 100 μm The presence of 1 or more patches of partial or complete depigmentation in the CFP that had 1 or more of the following: – Sharply demarcated borders seen in CFP or FA – Visibility of underlying choroidal vessels – "Excavated or punched-out" appearance on stereoscopy of color fundus photography or FA – Uniform hyperfluorescence bounded by sharp borders on late-phase angiography Minimum size criteria: greatest linear dimension ≥ 250 μm	113/1024; 11.0%	187/1024; 18.3%

(*Continued*)

Table 3. (Continued.)

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Grunwald et al[30]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg	PRN or monthly	Yes	CFP or FA	The presence of ≥1 patches of partial or complete depigmentation in the CFP that had ≥1 of the following: – Sharply demarcated borders seen in CFP or FA – Visibility of underlying choroidal vessels – "Excavated or punched-out" appearance on stereoscopy of color fundus photography or FA – Uniform hyperfluorescence bounded by sharp borders on late-phase angiography Minimum size criteria: greatest linear dimension ≥ 250 μm	120/1084; 11.1%	156/1084; 14.4%
Grunwald et al[35]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg	PRN or monthly	Yes	CFP or FA	The presence of ≥1 patches of partial or complete depigmentation in the CFP that had ≥1 of the following: – Sharply demarcated borders seen in CFP or FA – Visibility of underlying choroidal vessels – "Excavated or punched-out" appearance on stereoscopy of color fundus photography or FA – Uniform hyperfluorescence bounded by sharp borders on late-phase angiography Minimum size criteria: greatest linear dimension ≥ 250 μm	121/1011; 12.0%	172/1011; 17.0%

Table 3. (Continued.)

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Gune et al[9]	Ranibizumab 0.5 or 2 mg	PRN or monthly	No	SD-OCT	cRORA on OCT B-scans: – Increased signal transmission through the choroid (choroidal hypertransmission) – Attenuation of the RPE band – Collapse or thinning of the outer retinal layers Minimum size criteria: diameter ≥ 125 μm	NR	246/761; 32.3%
Koizumi et al[41]	Aflibercept 2 mg	Monthly in the first year followed by TREX	NA	FAF	Well-demarcated hypoautofluorescence inside the retinal vascular arcade Minimum size criteria: greatest linear dimension ≥ 250 μm	9/84; 10.7%	14/84; 16.7%
Mantel et al[37]	Ranibizumab 0.5 mg, aflibercept 2.0 mg	PRN with initial loading phase	No	FAF and CFP/FA/SD-OCT	Dark zone on FAF, with at least one of the following: – Increased visibility of the choroid on FA or CFP – Sharply demarcated increased choroidal reflectivity on SD-OCT with absence of the RPE line Minimum size criteria: greatest linear dimension ≥ 250 μm	NR	63/149; 42.3%
Sadda et al[36]	Ranibizumab 0.5 or 2 mg	PRN or monthly	No	CFP or FA	Sharply demarcated areas of RPE depigmentation with increased visibility of choroidal vessels through the lesion on CFP or FA, corresponding to flat areas of well-demarcated staining on FA Minimum size criteria: greatest linear dimension ≥ 250 μm	205/972; 21.1%	286/972; 29.4%
Sarraf et al[34]	Ranibizumab 0.5 or 2 mg	PRN or monthly	No	CFP or FA	Sharply demarcated areas of RPE depigmentation with increased visibility of choroidal vessels through the lesion on CFP or FA, corresponding to flat areas of well-demarcated staining on FA Minimum size criteria: greatest linear dimension ≥ 250 μm	NR	229/746; 30.7%

(*Continued*)

Table 3. (Continued.)

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Sato et al[43]	Aflibercept 2 mg	PRN with initial loading phase	NA	CFP or FA	Sharply demarcated areas of RPE depigmentation with increased visibility of choroidal vessels through the lesion on CFP or FA, corresponding to flat areas of well-demarcated staining on FA Minimum size criteria: greatest linear dimension ≥ 250 μm	NR	6/28; 21.4%
Sitnilska et al[38]	Ranibizumab 0.5 mg	PRN with initial loading phase	NA	CFP or SD-OCT	– CFP: sharply demarcated area of RPE depigmentation with increased visibility of choroidal vessels – SD-OCT: thinning of the RPE band with abrupt/sharp thickness loss and loss of overlying ellipsoid zone and external limiting membrane, accompanied by thinning of the outer nuclear layer Minimum size criteria: diameter ≥ 175 μm	15/52; 28.8%	21/52; 40.4%
Spooner et al[42]	Bevacizumab 1.25 mg, ranibizumab 0.5 mg, aflibercept 2 mg	PRN or TREX with initial loading dose	Yes	FAF and SD-OCT	– Sharp, delineated hypoauto fluorescence on FAF AND – Attenuation of the RPE band and loss of overlying ellipsoid zone and external limiting membrane with thinning of the outer nuclear layer, together with enhanced signal transmission into the choroid on OCT Minimum size criteria: area ≥ 0.02 mm^2	22/205; 10.7%	33/205; 16.1%

Table 3. (Continued.)

Study	Anti-VEGF Drug	Treatment Regimen	Switch among Drugs or Regimen Possible	Imaging Modality for Macular Atrophy Diagnosis	Criteria for Macular Atrophy Diagnosis	1-yr Macular Atrophy Incidence	2-yr Macular Atrophy Incidence
Staurenghi et al[48]	Ranibizumab 0.5 or 2 mg	PRN or monthly	No	SD-OCT	cRORA on OCT B-scans: – Increased signal transmission through the choroid (choroidal hypertransmission) – Attenuation of the RPE band – Collapse or thinning of the outer retinal layers Minimum size criteria: diameter ≥ 125 μm	NR	195/593; 32.9%

CFP = color fundus photography; cRORA = complete retinal pigment epithelium and outer retinal atrophy; FA = fluorescein angiography; FAF = fundus autofluorescence; ICGA = indocyanine green angiography; NIR = near-infrared reflectance; NR = not reported; PRN = pro re nata (as needed); RPE = retinal pigment epithelium; SD = standard deviation; SD-OCT = spectral-domain OCT; TD = time domain; TREX = treat-and-extend.

differently, our analysis demonstrated that also considering both clinical trial and routine clinical practice, roughly 1 out of every 3 patients with neovascular AMD develops macular atrophy within 2 years of initiating treatment.

This study also sought to stratify the incidence of macular atrophy across various types of MNV. Specifically, the incidence rates differed across MNV types: 26% for type 1/2 MNV and 49% for type 3 MNV at 24 months. In a prior study, Staurenghi et al[48] retrospectively analyzed the structural OCT findings of patients with neovascular AMD treated in the HARBOR trial. They demonstrated that type 3 MNV in the study eye constitutes a significant risk factor for the development of macular atrophy at the 24-month follow-up visit. Out of the 1097 patients enrolled in the HARBOR trial, 177 individuals exhibited evidence of type 3 MNV. Among them, 27 patients (15.3%) with type 3 MNV showed signs of macular atrophy in the study eye at baseline (i.e., before the initiation of anti-VEGF therapy). In cases with no detectable macular atrophy at baseline, 49.2% of these cases developed new macular atrophy by month 24. Hence, our systematic review and meta-analysis seem to validate that the incidence of macular atrophy varies among different types of MNV, with type 3 MNV exhibiting the highest incidence. One possible explanation for the increased incidence of macular atrophy in eyes with type 3 MNV could be the more severely impaired choriocapillaris in these cases.[53] In type 1 and type 2 MNV, the choriocapillaris retains enough functionality to support a neovascular response, which partially compensates for its nutritional role to the RPE and photoreceptors.[54,55] In contrast, in type 3 MNV, the choriocapillaris is significantly compromised, prompting RPE cells to leave their monolayer and extend toward the deep capillary plexus, leading to the formation of type 3 lesions.[53] Additionally, repeated anti-VEGF therapy often suppresses the intraretinal neovascular lesion in type 3 MNV, accelerating macular atrophy formation in the absence of vascular compensation.[56]

We observed significant heterogeneity among the studies we included, which we attempted to address to some extent through our meta-analysis. However, this heterogeneity could only be partially addressed by our analyses as we did not have access to raw data. Additionally, the prevalence and incidence estimates may vary widely because of differences in the diagnostic criteria used to define macular atrophy, and the diagnostic procedures varied across the studies we reviewed. The absence of OCT in several studies may have led to an underestimation of the incidence of macular atrophy (i.e., small regions of RPE atrophy may be overlooked in not-optimal quality fundus photographs, but detectable on structural OCT). Additionally, we did not have access to the patients' data, which prevented us from evaluating other significant associations, such as the relationship between the incidence of macular atrophy and the number of anti-VEGF injections. More importantly, this study included both clinical trials and real-world–setting studies. However, only 2 clinical trial studies were ultimately included in the meta-analysis, which prevented us from differentiating between the 2 settings in terms of macular atrophy. Another limitation is that the studies

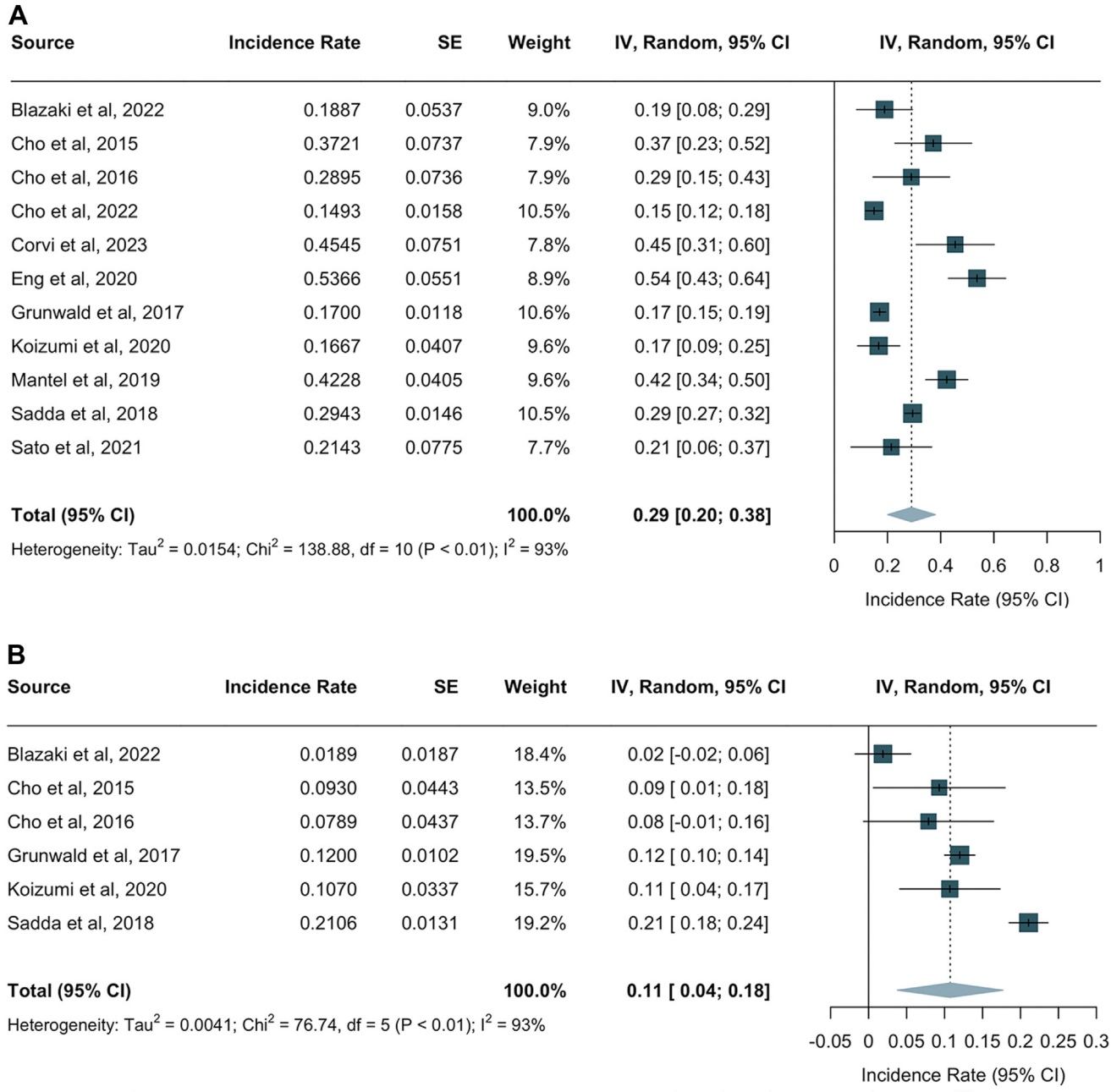

Figure 3. Forest plots of macular atrophy incidence after (**A**) 2 years and (**B**) 1 year of anti-VEGF therapy. In the graph, each study is represented by a separate row. For each study, the incidence rate of macular atrophy is displayed along with the standard error (SE) and the study's weight. On the right, a navy square is centered on the point estimate of the effect size, with a horizontal line (whiskers) extending on both sides of the square to represent the 95% confidence interval (CI) of the point estimate.

included in our analysis used different drugs, and we cannot completely rule out variations in incidence rates based on the drug used. However, there is currently insufficient evidence to support significant heterogeneity in incidence rates related to the type of drug. Nonetheless, as mentioned above, it is worth noting that the incidence rates observed in our analysis are very similar to those reported in clinical trials. Also, we made some postregistration modifications to the study methodology compared with our submitted PROSPERO protocol. Initially, we planned to use the Newcastle-Ottawa scale to assess the risk of bias across all included studies. However, upon further reflection, we decided that using separate tools for randomized and non-randomized studies would provide a more precise quality assessment. Additionally, because of insufficient data on the time to atrophy from treatment initiation and the incidence of atrophy in patients treated with specific anti-VEGF agents, we were unable to further analyze these aspects as

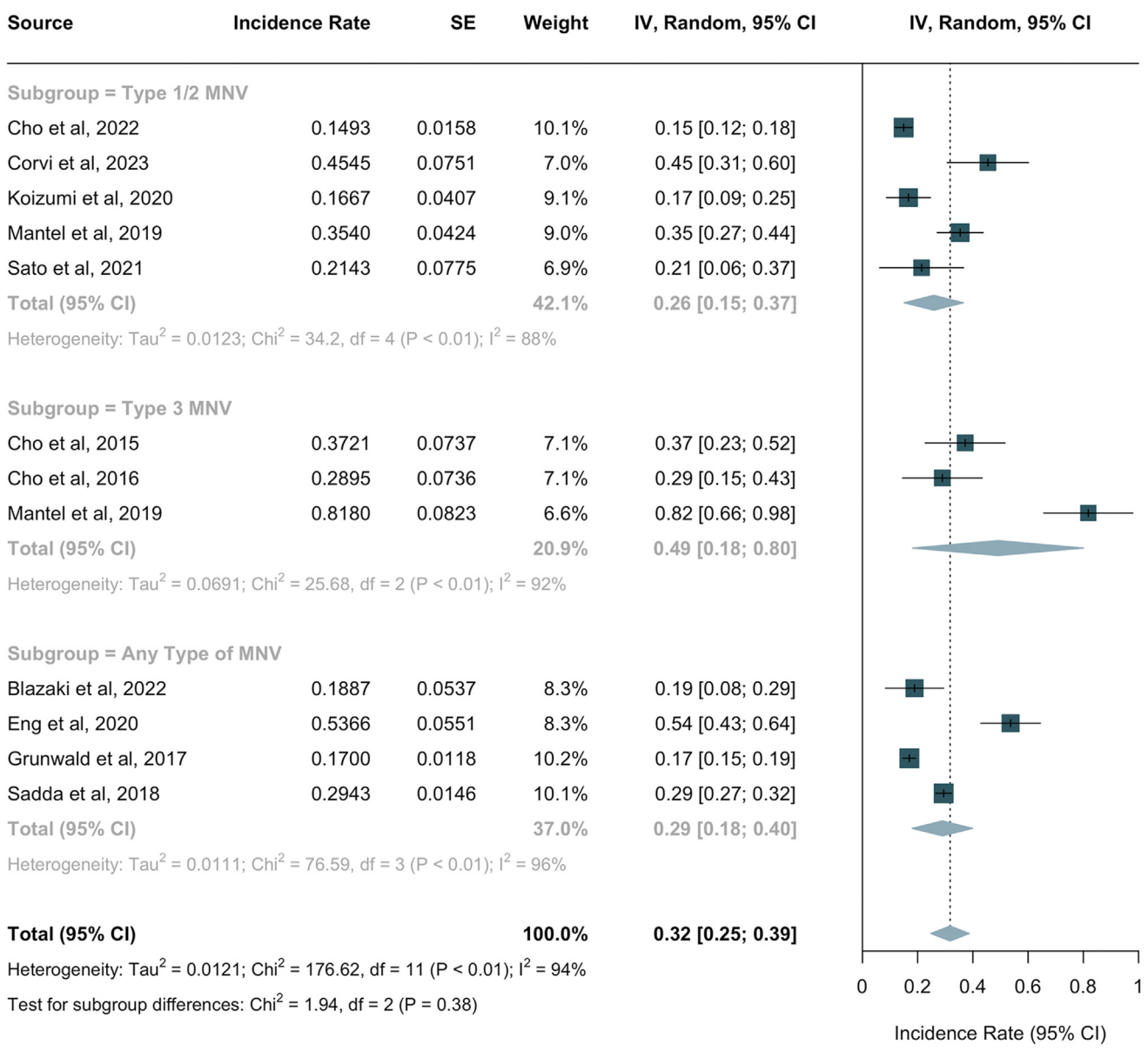

Figure 5. Forest plots of macular atrophy incidence after 2 years by macular neovascularization (MNV) type. In the graph, each study is represented by a separate row. For each study, the incidence rate of macular atrophy is shown, along with the standard error (SE) and the study's weight. On the right, a navy square is centered on the point estimate of the effect size, with a horizontal line (whiskers) extending on both sides of the square to represent the 95% confidence interval (CI) of the point estimate. The studies are organized according to the type of MNV evaluated.

initially intended. Lastly, we included only studies published in English, which may have limited the number of studies eligible for inclusion.

In summary, our systematic review and meta-analysis confirm that macular atrophy is a common early complication in patients with neovascular AMD receiving anti-VEGF therapy. Notably, our analysis found that about 1 in 3 patients with neovascular AMD without macular atrophy at baseline develop this complication within 2 years of starting treatment. Furthermore, our analysis underscores the variability in macular atrophy incidence across MNV types, with type 3 MNV displaying the highest incidence. These findings should be considered in light of certain limitations, including the moderate certainty of evidence due to risks of bias in nonrandomized studies, high heterogeneity among results, and variability in imaging modalities used to diagnose macular atrophy. Despite these challenges, our results underscore the need for innovative therapeutic strategies to reduce macular atrophy incidence in this population.

Footnotes and Disclosures

Originally received: October 16, 2024.
Final revision: January 2, 2025.
Accepted: January 13, 2025.
Available online: January 20, 2025. Manuscript no. ORET-D-24-00944R2.

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures:

F.B.: Consultant − AbbVie, Alimera, Bayer, Boehringer Ingelheim, Fidia Sooft, Hofmann La Roche, Novartis, NTC Pharma, Oxurion Nv, Sifi.

M.R.: Consultant, Payment or honoraria − AbbVie, Bayer, Hofmann La Roche, Novartis, Zeiss; Data Safety Monitoring Board or Advisory Board member − AbbVie, Bayer, Hofmann La Roche.

E.B.: Consultant, Payment or honoraria − AbbVie, Bayer, Hofmann La Roche, Novartis, Zeiss; Data Safety Monitoring Board or Advisory Board member − AbbVie, Bayer, Hofmann La Roche.

The other authors have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS: No human subjects were included in this study. The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024474924). This study is a systematic review and meta-analysis that does not involve human subjects, and did not require IRB approval. This study adhered to the Declaration of Helsinki. Individual patient-level consent was not required.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Berni, Coletto, Bandello, Reibaldi, Borrelli

Analysis and interpretation: Berni, Coletto, Li, Shen, Bandello, Reibaldi, Borrelli

Data collection: Berni, Coletto, Li, Shen, Bandello, Reibaldi, Borrelli

Obtained funding: N/A

Overall responsibility: Berni, Coletto, Borrelli

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CFP** = color fundus photography; **CI** = confidence interval; **FA** = fluorescein angiography; **FAF** = fundus autofluorescence; **MNV** = macular neovascularization; **RCT** = randomized controlled trial; **RPE** = retinal pigment epithelium; **SD-OCT** = spectral-domain OCT.

Keywords:
Anti-VEGF therapy, Macular atrophy, Macular complications, Neovascular age-related macular degeneration, Poor visual outcome.

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