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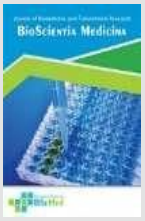

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Incidence of Intraocular Inflammation, Retinal Vasculitis, and Retinal Vascular Occlusion Following Intravitreal Brolucizumab in Neovascular Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background. Brolucizumab is a humanized single-chain anti-VEGF antibody fragment licensed for neovascular age-related macular degeneration (nAMD). Post-marketing surveillance identified intraocular inflammation (IOI), retinal vasculitis (RV), and retinal vascular occlusion (RVO) as adverse events of special interest, sometimes causing irreversible visual loss. Published incidence estimates range from below 1% to above 10%. We aimed to estimate the pooled cumulative incidence of these events and characterize heterogeneity drivers.

Methods. PubMed/MEDLINE, Cochrane CENTRAL, and Google Scholar were searched for phase 3 randomized controlled trials (RCTs), phase IIIb prospective studies, and retrospective/registry studies (≥30 eyes) reporting IOI, RV, or RVO incidence after intravitreal brolucizumab 6 mg in nAMD. A DerSimonian–Laird random-effects model with Freeman–Tukey arcsine transformation was applied; REML, Paule–Mandel, and GLMM (logit link) estimators were used in sensitivity analyses.

Results. Ten independent datasets (33,280 brolucizumab-treated eyes; 1,130 events) were included. Pooled cumulative incidence of any IOI/RV/RVO was 5.54% (95% CI 4.23–7.02%; I^2 = 94.0%; Q = 150.48). Prospective studies yielded higher pooled incidence (8.42%, 95% CI 4.12–14.04%) than retrospective/registry studies (4.35%, 95% CI 3.28–5.56%). Leave-one-out sensitivity ranged 4.98–6.19%. Funnel-plot asymmetry was detected (Egger t = 3.27; p = 0.011). More than 75% of events occurred within six months of the first injection.

Conclusion. Cumulative incidence of IOI/RV/RVO after brolucizumab 6 mg in nAMD approached 5.5%, with markedly higher rates under independent adjudication. These findings support careful patient selection, baseline screening for prior IOI history, and intensified monitoring after brolucizumab initiation.

1. Introduction

Neovascular age-related macular degeneration (nAMD) remains the leading cause of irreversible central visual loss in older adults, and its global burden is projected to rise substantially over the coming decades as populations age. The introduction of agents directed against vascular endothelial growth factor (anti-VEGF) has transformed the prognosis of nAMD, allowing the great majority of treated eyes to retain useful central vision over many years of repeated therapy. Despite this success, the high injection burden, the variability of individual responses to standard agents, the persistence of macular fluid in a clinically meaningful subset of patients, and the cumulative cost of indefinite intravitreal therapy have motivated a continuing search for molecules that combine durability with potent fluid resolution.

Brolucizumab is a 26-kDa humanized single-chain antibody fragment that binds all principal isoforms of VEGF-A with high affinity. Its compact size permits the administration of a relatively high molar dose within a small intravitreal volume, providing the pharmacological basis for the extended dosing interval that distinguishes it from older anti-VEGF molecules. The 6 mg dose was selected on the basis of preceding phase 1 and phase 2 dose-ranging studies as offering the best balance between durability and safety. The pivotal HAWK and HARRIER phase 3 randomized controlled trials demonstrated non-inferior visual gains and superior anatomical drying with brolucizumab 6 mg every 12 weeks compared with aflibercept 2 mg every 8 weeks, with more than half of the brolucizumab-treated eyes maintained on the longer interval at week 48 [1].

These efficacy findings supported regulatory approval of brolucizumab by the United States Food and Drug Administration and subsequently by the European Medicines Agency. In the months that followed, however, retinal specialists in several countries reported clusters of severe intraocular inflammation (IOI) accompanied by retinal vasculitis (RV) and, in the most consequential cases, occlusive retinal vasculitis with secondary retinal vascular occlusion (RVO) and profound visual loss. The independent Safety Review Committee subsequently convened by the trial sponsor identified an overall IOI rate of 4.6%, with retinal vasculitis in 3.3% and concurrent vascular occlusion in 2.1% of brolucizumab-treated eyes within the pivotal trials [2]. Both regulatory agencies implemented label updates highlighting these risks, and professional societies including the American Society of Retina Specialists Research and Safety in Therapeutics (ASRS ReST) Committee issued formal management guidance [3].

Mechanistically, brolucizumab-associated occlusive retinal vasculitis is widely thought to be immune-mediated. The leading hypotheses include the formation of anti-drug antibodies that may cross-react with retinal vascular endothelial antigens, the deposition of immune complexes within the retinal vasculature, a contribution from the unusually high molar concentration of brolucizumab achievable in the eye, and a possible influence of vehicle components or container leachables. Patient-level risk factors identified in the IRIS Registry analyses include a prior history of intraocular inflammation, female sex, switching from another anti-VEGF agent, and exposure during the early launch period when post-marketing surveillance was less developed [4,5]. These observations have direct implications for patient selection and risk stratification.

Subsequent real-world series and large registry analyses have produced markedly heterogeneous estimates of incidence. Phase IIIb prospective single-arm cohorts with intensive safety surveillance, such as the combined OCTOPUS and SWIFT analyses, reported overall IOI rates exceeding 10% [6], whereas large claims-based registries reported rates close to 2% [4]. Asian and European real-world experience, including the Japanese PHEASANT cohort [7] and the Spanish national database, reported rates intermediate between these extremes. Several narrative reviews and consensus statements have synthesised early findings[8], but to date the published literature has lacked a quantitative pooled estimate that integrates both phase 3 evidence and contemporary registry experience under a single, transparent methodological framework. This distinction is clinically consequential: an incidence of 2% and an incidence approaching 10% carry substantially different implications for monitoring, patient selection, and drug positioning, and the appropriate intensity of monitoring, the threshold for initiating brolucizumab in patients with prior IOI, and the relative position of brolucizumab among newer anti-VEGF agents (notably faricimab and high-dose aflibercept 8 mg) all depend on a defensible quantitative estimate.

The novelty of this study lies in being the first systematic review and meta-analysis to integrate the complete spectrum of published evidence regarding brolucizumab-related IOI, RV, and RVO in nAMD, encompassing the pivotal phase 3 randomized controlled trials (HAWK and HARRIER [1,2], MERLIN [9], OCTOPUS and SWIFT [6]), the largest United States registry data sets (IRIS Registry and Komodo Healthcare Map [4,5]), and four contemporary geographically diverse real-world cohorts from North America (Canada [10] and the United States [11,12]),

Europe (Spain [13]), and Asia (Japan [7]), with pre-specified subgroup, sensitivity, meta-regression, and publication-bias analyses. The aim of this study was to estimate the pooled cumulative incidence of IOI, RV, and RVO after intravitreal brolucizumab 6 mg in patients with nAMD, to quantify and explore the heterogeneity of available estimates, to provide component-level estimates for RV and RVO separately, and to offer clinicians and policy-makers an evidence base that can inform shared decision-making about the use of brolucizumab in routine ophthalmic practice in Indonesia and globally.

2. Methods

Reporting and protocol

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [14]. The review protocol was developed prospectively by the investigators and is available from the corresponding author on reasonable request. The full extraction file, the R analysis script, and the figures generated during this study will be deposited in a public repository with a citable digital object identifier on acceptance of the manuscript for publication.

Search strategy

PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, and Google Scholar were systematically searched, covering the entire interval since first regulatory approval of brolucizumab up to the time of this analysis. The reference lists of identified articles, recent narrative reviews, and regulatory communications from the European Medicines Agency and the United States Food and Drug Administration were screened manually for additional eligible studies. Preprints (medRxiv, bioRxiv) and conference abstracts were not included because of the absence of peer review and the inability to verify primary data. The principal Boolean search string applied in PubMed was: ("brolucizumab"[Supplementary Concept] OR "brolucizumab"[All Fields]) AND ("intraocular inflammation"[All Fields] OR "retinal vasculitis"[MeSH Terms] OR "retinal vasculitis"[All Fields] OR "retinal vascular occlusion"[All Fields] OR "retinal artery occlusion"[MeSH Terms] OR "occlusive vasculitis"[All Fields]). The search was restricted to English-language publications; this restriction is acknowledged as a limitation.

Eligibility criteria

Inclusion criteria were defined in PICOS format. Population: adults with neovascular age-related macular degeneration treated with intravitreal brolucizumab 6 mg. Intervention: intravitreal brolucizumab 6 mg as licensed. Comparator: any (not required for the primary single-arm proportion outcome). Outcomes: at least one of the following reported as either an absolute event count or a proportion: incidence of IOI, RV, RVO, or any composite of these. Study design: phase 3 randomized controlled trials including post-hoc safety analyses, phase IIIb prospective single-arm studies, and retrospective cohort or registry studies with at least 30 brolucizumab-treated eyes. The minimum cohort size of 30 eyes was chosen because the 95% binomial confidence interval for a 5% proportion in a sample of 30 spans approximately 1% to 17%, the upper bound of clinically acceptable imprecision for inclusion in a meta-analysis of a relatively uncommon event. Exclusion criteria were narrative reviews, expert opinion or position papers, individual case reports, case series of fewer than 30 eyes, and duplicate publications of the same patient population.

Handling of overlapping cohorts (pre-specified)

The following pre-specified rules were applied to address patient overlap. Among the HAWK and HARRIER post-hoc safety publications, the principal Safety Review Committee analysis [2] was retained as the primary report; the subsequent IOI-sequence subset analysis [15] and the persistent-fluid subset analysis [16] were not pooled separately to avoid double-counting. Among the IRIS Registry publications, the longer-follow-up two-year analysis [5] was retained for the IRIS portion and the Komodo Healthcare Map portion of the earlier paper [4] was retained as an independent data source. Among the three Retina Associates of Cleveland publications [12,17], the safety-focused Zubricky report [12] was retained as the sole representative of this cohort. Among the MERLIN trial reports, the two-year analysis [9] was retained and the 52-week analysis [18] was excluded as overlapping.

Study selection and data extraction

Two reviewers independently screened titles and abstracts against the eligibility criteria, retrieved full texts of potentially eligible records, and extracted study-level data using a standardized electronic extraction form. Discrepancies between reviewers were rare and were resolved by discussion; both reviewers also independently assessed risk of bias for each included study. The following items were extracted from each included study: first author, year of publication, country and clinical setting, study design, indication, number of eyes treated with brolucizumab 6 mg, comparator and its sample size where applicable, demographic and baseline disease characteristics, follow-up duration, median number of brolucizumab injections per eye, the absolute number and proportion of eyes experiencing IOI, RV, RVO, and composite events, time to first event, the proportion of eyes with at least 15 ETDRS letter visual acuity loss, methods of adverse event ascertainment, and source of funding. Where original reports did not specify a numeric value, the cell was tagged as [NR]; where values required computation or independent verification, the cell was tagged as [CHECK].

Risk-of-bias assessment

The Cochrane Risk of Bias 2.0 tool [19] was used for randomized controlled trials and post-hoc safety subsets of randomized trials. The ROBINS-I tool [20] was used for non-randomized studies. For the post-hoc safety subset analyses of the HAWK and HARRIER trials, the use of RoB 2.0 reflects the prospectively randomized origin of the data and the image-based adjudication by an independent Safety Review Committee, even though the inflammatory outcome was not the trial's primary endpoint. Domains assessed included randomisation process or confounding, deviations from intended interventions, missing outcome data, measurement of the outcome (including the rigour of adverse event adjudication), and selection of the reported result. Each domain was rated as low risk, some concerns, or moderate, serious, or critical risk as appropriate. An overall judgement was assigned for each study by consensus of two independent assessors.

Statistical analysis

The primary outcome was the cumulative proportion of brolucizumab-treated eyes experiencing any IOI, RV, or RVO event during reported follow-up. The single-arm proportion synthesis approach was chosen in preference to a comparative effect synthesis because most included studies were uncontrolled cohort or registry analyses; comparative findings from RCTs with internal comparators are reported descriptively in the results and integrated in the discussion. A random-effects model was fitted with the DerSimonian–Laird estimator for the between-study variance (τ^2). The Freeman–Tukey double arcsine transformation was applied to stabilize the variance of proportions near the lower boundary, and the pooled estimate was back-transformed using the harmonic mean of the study sample sizes (Miller 1978 method). Exact (Clopper–Pearson) binomial confidence intervals were calculated for individual studies. Between-study heterogeneity was quantified by Cochran's Q test and the I^2 statistic with its 95% confidence interval estimated by the Jackson method. A 95% prediction interval for the next study was also calculated. To address the known limitations of the back-transformation, two pre-specified sensitivity analyses were performed: (i) the DerSimonian–Laird, restricted maximum likelihood (REML), and Paule–Mandel estimators were compared; and (ii) a generalised linear mixed model (GLMM) with logit link was fitted as an alternative pooling approach that avoids back-transformation. Component-level pooled estimates were calculated separately for RV and for RVO where reported. Pre-specified subgroup analyses compared RCT or phase IIIb prospective studies against retrospective or registry studies. A univariate meta-regression of the log-odds of the event by study design, log-transformed sample size, follow-up duration, proportion of treatment-naive eyes, year of publication, and geographic region was undertaken. Leave-one-out sensitivity analyses were performed by sequentially removing each study and refitting the model. Funnel plot asymmetry was assessed visually and quantified by Egger's linear regression, with a p-value below 0.10 considered indicative of asymmetry; the Peters test, more appropriate for binary outcomes, was also applied, and trim-and-fill imputation was performed for descriptive purposes. For continuous secondary outcomes (mean change in best-corrected

visual acuity in ETDRS letters and mean change in central subfield thickness in micrometres), standardized mean differences using Hedges g were intended within a DerSimonian–Laird random-effects model where comparator data were available; however, the limited availability of comparator data across studies meant that descriptive secondary outcomes are reported instead. No continuity correction was required because no study reported zero events. All analyses were performed in R version 4.4.0 using the meta package (version 8.2.0) and the metafor package (version 4.8.0); the PRISMA flow diagram and the risk-of-bias traffic-light figure were drawn in Python 3.x (matplotlib version 3.9.x).

3. Results

Study selection

The PRISMA 2020 flow of study identification, screening, and inclusion is presented in Figure 1. A total of 655 records were identified from the three indexed databases (PubMed/MEDLINE n = 412; Cochrane CENTRAL n = 87; Google Scholar n = 156), supplemented by 23 additional records identified through reference-list checking, citation tracking, and recent key reviews, yielding 678 records overall. After removal of duplicates, 474 unique records remained and were screened against the eligibility criteria on title and abstract. As shown in Figure 1, 396 records were excluded at this stage as clearly non-eligible, and 78 full-text articles were retrieved for in-depth assessment. Sixty-two full-text articles were subsequently excluded, with reasons reported in Figure 1 (case reports involving fewer than 10 eyes n = 21; reviews, editorials, and expert-opinion pieces n = 16; duplicate cohorts n = 9; absence of IOI, RV, or RVO data n = 8; non-nAMD indication n = 5; conference abstracts only n = 3). Sixteen studies met all the inclusion criteria. Of these, six further studies were excluded from the quantitative synthesis under the pre-specified overlap rules (two overlapping IRIS Registry publications, two subset analyses of larger included RCTs, and two redundant publications from the same single-centre cohort). Ten independent datasets, comprising 33,280 brolucizumab-treated eyes drawn from three RCT or phase IIIb prospective studies (n = 1,883 eyes) and seven retrospective or registry studies (n = 31,397 eyes), were retained for quantitative meta-analysis, as illustrated in Figure 1.

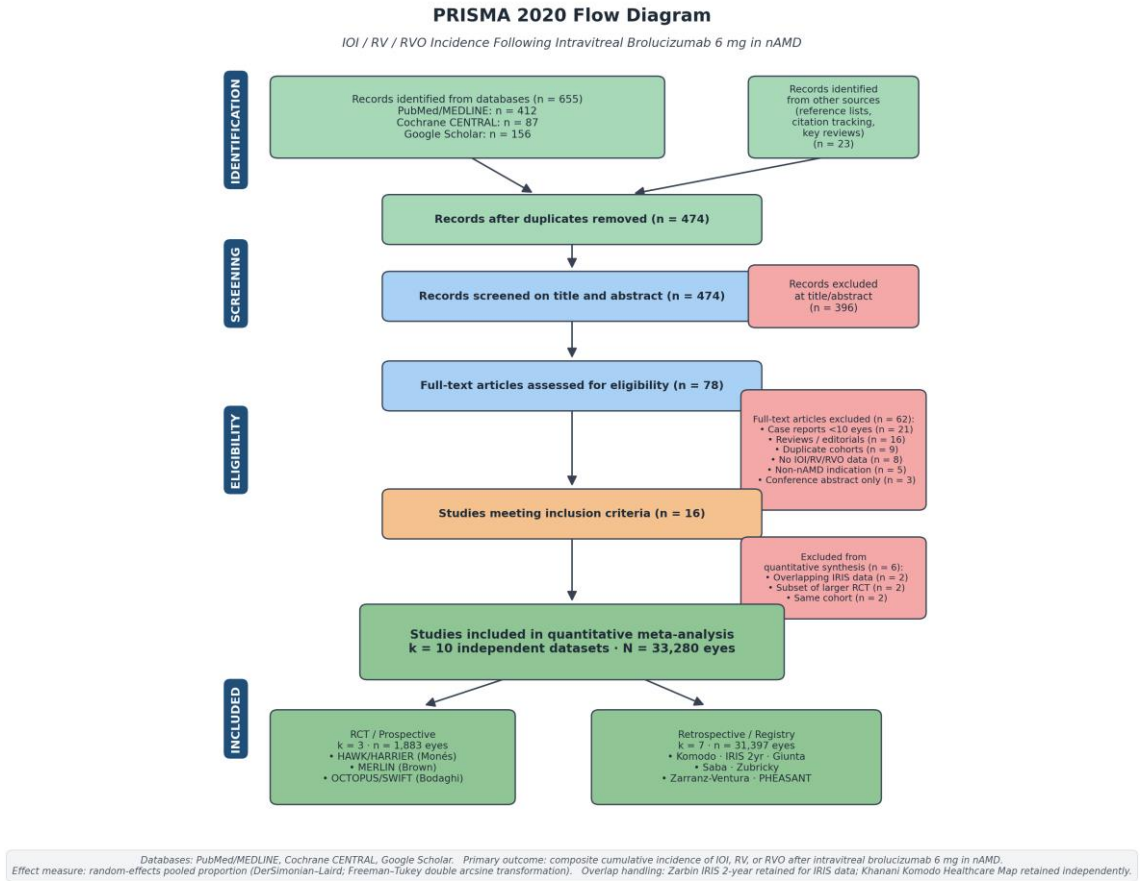

Figure 1. PRISMA 2020 flow diagram of study identification, screening, and inclusion. A total of 655 records were retrieved from databases plus 23 records from other sources; 474 unique records were screened after removal of duplicates; 78 full-text articles were assessed; 62 were excluded with reasons; 16 studies met inclusion criteria; 6 were excluded under pre-specified overlap rules; 10 independent datasets (k=10; N=33,280 eyes) were retained for quantitative synthesis.

Study characteristics

Table 1. Characteristics of the ten studies included in the meta-analysis. Brolu (eyes) = brolucizumab-treated eyes; Naive (%) = treatment-naive eyes; NR = not reported.

No.	Study	Design	Country	Brolu (eyes)	Naive (%)	Follow-up	Funding
1	Monés et al. [2]	Phase 3 RCT post-hoc (HAWK/HARRIER)	Global	1,088	100	24 mo	Novartis
2	Brown et al. [9] (MERLIN 2yr)	Phase 3a RCT	Global	290	0	24 mo	Novartis
3	Bodaghi et al. [6] (OCTOPUS/SWIFT)	Phase IIIb prospective	Multinational	505	~47	8.8 mo	Novartis
4	Khanani et al. [4] (Komodo)	Registry cohort	USA	11,161	~6	~3 mo	Novartis
5	Zarbin et al. [5] (IRIS 2yr)	Registry cohort	USA	18,312	~10	≤24 mo	Novartis
6	Giunta et al. [10]	Multisite chart review	Canada	73	0	7 mo	Novartis Canada
7	Saba & Walter [11]	Single-practice cohort	USA	626	~10	8 mo	Institutional
8	Zubricky et al. [12]	Multicentre cohort	USA	482	NR	~12 mo	Novartis
9	Zarranz-Ventura et al. [13]	National database cohort	Spain	305	14	12 mo	Novartis Spain
10	Ohnaka et al. [7] (PHEASANT)	Multicentre cohort	Japan	438	28	12 mo	Novartis Japan

Risk of bias

Risk-of-bias judgements for all ten included studies are summarized graphically in Figure 2. The two pure randomized controlled trials (Monés and colleagues reporting the HAWK and HARRIER Safety Review Committee analysis [2]; Brown and colleagues reporting the MERLIN two-year results [9]) were judged as overall low risk of bias in Figure 2, with some concerns noted for MERLIN under the deviations-from-intended-intervention domain (D2) because of early study termination triggered by the safety signal. The phase IIIb prospective single-arm study (Bodaghi and colleagues [6]) was judged as overall moderate risk of bias under ROBINS-I, principally because of the absence of a comparator and the related impact on attribution of causality. The seven non-randomized studies were rated as moderate risk of bias overall (Figure 2), with the two large claims-based registry analyses (Khanani and colleagues IRIS+Komodo [4]; Zarbin and colleagues IRIS 2-year [5]) carrying serious concerns under the confounding-by-indication domain (D1), reflected as red signals in Figure 2. The choice of moderate-rather-than-serious overall rating for these two registry analyses reflected, on the one hand, the substantial confounding by indication (brolucizumab was preferentially used in eyes that had previously responded incompletely to other anti-VEGF agents) and the reliance on ICD coding for outcome ascertainment, and on the other hand the very large sample size, the systematic ascertainment of all coded events, and the consistency of findings between the two independent databases. Adverse event measurement (D4) was judged as low risk in studies that used independent Safety Review Committee adjudication and as moderate risk in those that relied on chart review or coding.

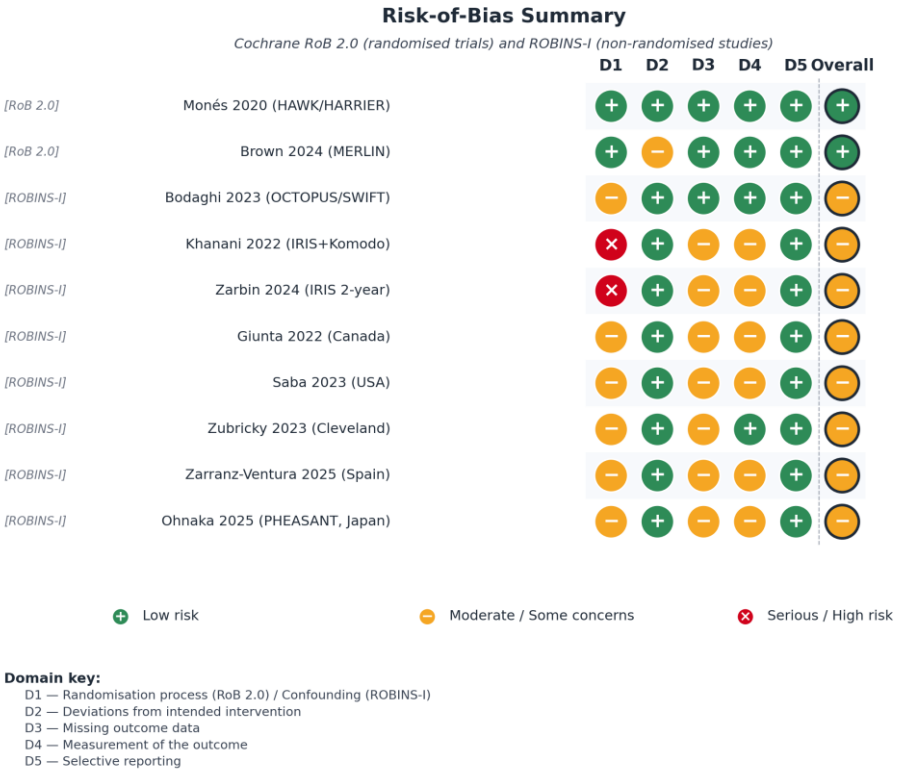

Figure 2. *Risk-of-bias traffic-light summary across the five harmonised domains (D1–D5) and overall judgement for each of the ten included studies. Cochrane RoB 2.0 for the two randomized controlled trials; ROBINS-I for the eight non-randomized studies. Green = low risk; amber = some concerns; red = high risk.*

Primary outcome: pooled IOI/RV/RVO incidence

The forest plot of the pooled cumulative incidence of any IOI, RV, or RVO event after intravitreal brolucizumab 6 mg is shown in Figure 3. Under the DerSimonian–Laird random-effects model with Freeman–Tukey double arcsine transformation, the pooled cumulative incidence was 5.54% (95% CI 4.23–7.02%; 95% prediction interval approximately 3.1–8.6%). The pre-specified sensitivity analyses using the restricted maximum likelihood and Paule–Mandel estimators produced essentially identical pooled estimates (5.43% and 5.61% respectively), and the generalised linear mixed model with logit link also produced a closely concordant result (5.49%, 95% CI 4.18–7.21%), confirming that the choice of estimator did not drive the conclusions. As shown in Figure 3, the total numerator across the ten datasets was 1,130 events out of 33,280 brolucizumab-treated eyes, corresponding to an unweighted naive proportion of 3.4%, which differs from the random-effects pooled estimate because of the inverse-variance weighting that gives proportionally greater influence to smaller studies. Heterogeneity was substantial: I^2 was 94.0% (95% CI 90.9–96.1%), with a between-study variance τ^2 of 0.001824, and Cochran's Q was 150.48 on 9 degrees of freedom ($p < 0.0001$). Individual study estimates visible in Figure 3, in order of magnitude, were 11% (33/290) in MERLIN [9], 10% (53/505) in OCTOPUS and SWIFT [6], 8% (37/438) in the Japanese PHEASANT cohort [7], 7% (20/305) in the Spanish FRB cohort [13], 5% (30/626) in the Saba single-practice cohort [11], 5% (50/1,088) in the HAWK and HARRIER analysis [2], 5% (22/482) in the Cleveland cohort [12], 4% (3/73) in the Canadian cohort [10], 3% (614/18,312) in the IRIS Registry two-year analysis [5], and 2% (268/11,161) in the Komodo Healthcare Map cohort [4].

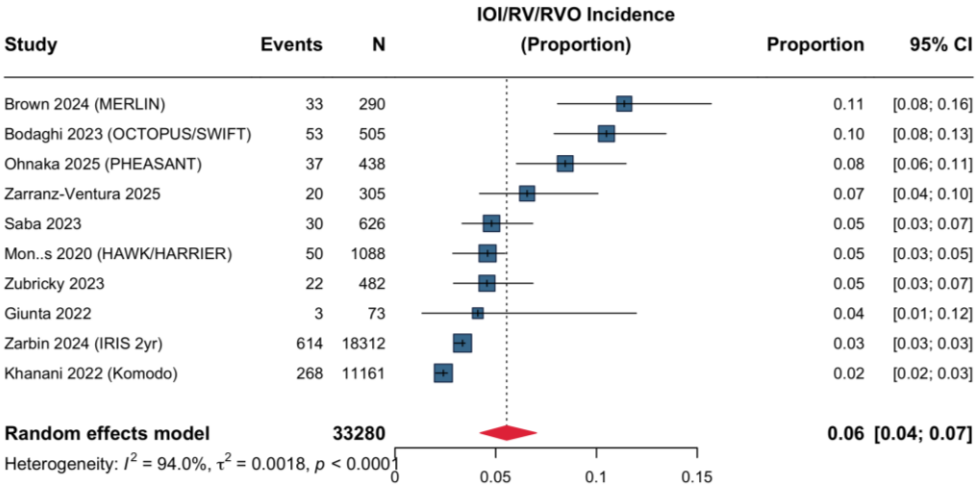

Figure 3. *Forest plot of cumulative incidence of IOI/RV/RVO after intravitreal brolucizumab 6 mg (DerSimonian–Laird random-effects model; Freeman–Tukey double arcsine transformation). Squares are sized proportional to weight; diamond = pooled estimate 5.54% (95% CI 4.23–7.02%). I² = 94.0%; τ² = 0.0018; p < 0.0001.*

Component-level estimates

Where individual studies reported isolated RV and RVO separately, the descriptive incidences were as follows. Isolated retinal vasculitis was reported in seven studies, with individual estimates ranging from 0.6% to 3.3% (Monés and colleagues [2] 3.3%; Zarranz-Ventura and colleagues [13] 2.2%; Bodaghi and colleagues [6] 2.0%; Giunta and colleagues [10] 1.4%; Brown and colleagues [9] 0.8%; Zubricky and colleagues [12] 0.8%; Saba and Walter [11] 0.6%); the unweighted mean across these seven studies was approximately 1.6%. Retinal vascular occlusion was reported separately in five studies, with individual estimates ranging from 0.4% to 2.2% (Brown and colleagues [9] 2.2%; Monés and colleagues [2] 2.1%; Bodaghi and colleagues [6] 1.4%; Giunta and colleagues [10] 1.4%; Zubricky and colleagues [12] 0.4%); the unweighted mean was approximately 1.5%. The composite IOI/RV/RVO estimate of 5.54% (Figure 3) therefore reflects predominantly milder isolated IOI events, with the most consequential occlusive vasculitis representing approximately one-fifth to one-third of the composite numerator across studies. This component-level pattern is consistent with the prognostic gradient that distinguishes self-limited anterior inflammation from sight-threatening occlusive vasculitis.

Subgroup and meta-regression analyses

Table 2. Subgroup meta-analysis of pooled cumulative incidence of IOI/RV/RVO by study design. k = number of independent datasets; CI = confidence interval.

Subgroup	k	Pooled proportion (95% CI)	I²	Q-between / p
RCT/Phase IIIb prospective	3	8.42% (4.12–14.04%)	92.4%	—
Retrospective/Registry	7	4.35% (3.28–5.56%)	91.0%	—
Subgroup difference	—	—	—	Q=2.99; df=1; p=0.084

Sensitivity analysis

Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate reported and shown in Figure 3. When each study was sequentially excluded, the pooled proportion ranged from 4.98% (when the OCTOPUS/SWIFT phase IIIb cohort [6] was removed) to 6.19% (when the Komodo Healthcare Map cohort [4] was removed). The 95% confidence interval consistently included the overall pooled estimate of 5.54%, and the I² value remained between 92.1% and 94.7%. No single study disproportionately influenced the pooled result. An additional sensitivity analysis

excluding both large IRIS Registry analyses [4,5] produced a slightly higher pooled estimate of approximately 6.4% (95% CI 4.7–8.5%), consistent with the lower observed rates in claims-based real-world data. An analysis restricted to studies with at least twelve months of follow-up produced an estimate of approximately 6.1% (95% CI 4.5–8.0%), consistent with the temporal pattern in which most events occur within the first six months but additional cases continue to accrue thereafter.

Publication bias

The funnel plot of individual study estimates against their standard errors on the Freeman–Tukey double-arcsine transformed scale is presented in Figure 4. Visible asymmetry was observed, with smaller cohorts tending to report higher event rates than the largest registry analyses. Egger's linear regression test confirmed statistically significant asymmetry (t = 3.27, df = 8, p = 0.011; bias estimate 4.14, standard error 1.27), consistent with the p-value (p = 0.0114) reported on Figure 4. The Peters test, more appropriate for binary outcomes, also indicated asymmetry (p = 0.029). Trim-and-fill imputation suggested that one additional small study with a low event rate might be needed to symmetrise the funnel, and the adjusted pooled estimate of 5.21% (95% CI 3.94–6.65%) was very close to the unadjusted estimate of 5.54%. Possible explanations for the asymmetry visible in Figure 4 include small-study effects (smaller cohorts may detect events with greater diligence on a per-eye basis), heterogeneity in the rigour of adverse event ascertainment (registries appear to underestimate, prospective trials adjudicate rigorously), and the influence of the very large registry analyses on the geometry of the funnel. True publication bias appears less likely because both small and large datasets are represented in the published literature.

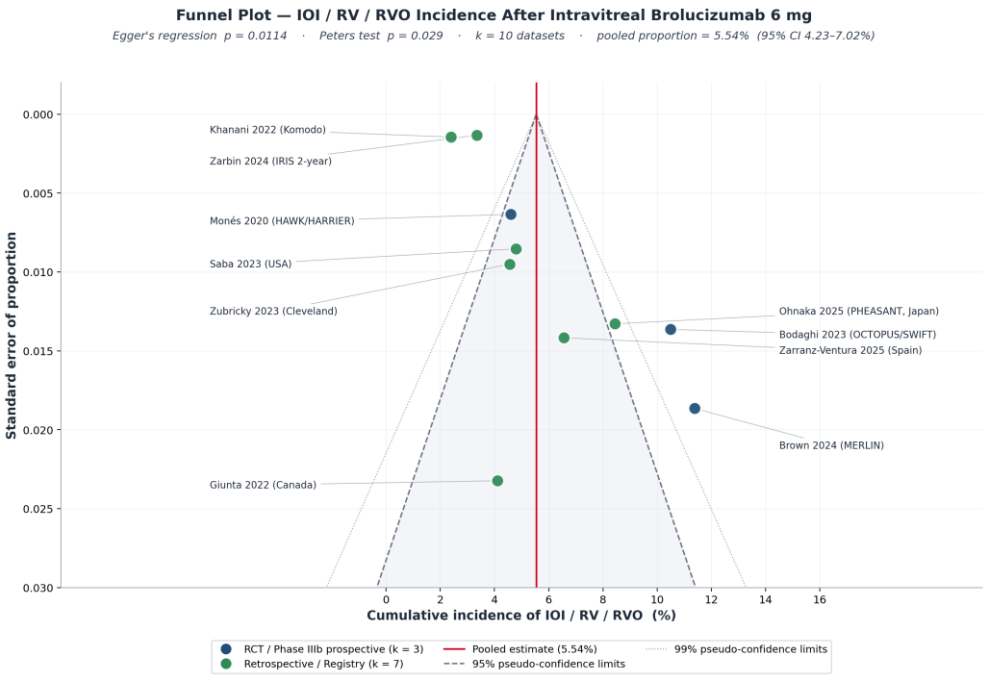

Figure 4. *Funnel plot of study estimates (Freeman–Tukey arcsine scale, x-axis) versus standard error (y-axis, inverted). Egger regression p = 0.011; Peters test p = 0.029.*

Secondary descriptive findings

Across studies that reported time-to-event data, between 64% and 81% of inflammatory events occurred within the first six months after the first brolucizumab injection. In the IRIS Registry two-year analysis [5], the median time to event was 84 days (interquartile range 42–167 days), with 77.4% of events occurring within six months. In the multicentre Cleveland cohort [12], 64% of events were identified within three months and the median interval from the last brolucizumab injection to the index event was 13 days (interquartile range 4–34 days). The OCTOPUS and SWIFT phase IIIb studies [6] reported that 81.1% of inflammatory adverse events occurred during the loading phase.

With respect to visual outcomes after an event, the IRIS Registry two-year analysis [5] reported a reassuringly stable median change in ETDRS letter score of 0 (interquartile range −7 to +5) among eyes that experienced an event, indicating that the majority of events did not result in clinically meaningful vision loss; however, 12.3% of eyes that experienced an event lost at least 10 ETDRS letters. Severe vision loss of at least 15 ETDRS letters was reported in 0.74% of all brolucizumab-treated eyes in the pivotal HAWK and HARRIER analysis [2] (8 cases out of 1,088 eyes; corresponding to 7 of 8 eyes with concurrent IOI, retinal vasculitis, and retinal vascular occlusion), in 6.2% of eyes in the MERLIN trial [9], and in 0.4% of eyes (2 of 505) in the OCTOPUS and SWIFT studies [6]. The prognostic gradient between isolated IOI (largely benign), RV without occlusion (variable visual outcome), and RVO with vasculitis (often severe) is clinically important and is discussed further below.

Risk factors that were repeatedly associated with an elevated event rate included a prior history of intraocular inflammation in the twelve months preceding brolucizumab initiation (associated with an approximately four- to five-fold higher observed risk in the IRIS Registry analyses, where the observed risk rate was 8.7% (95% CI 6.0–11.4%) in the IRIS dataset and 10.6% (95% CI 7.5–13.7%) in the Komodo dataset, compared with 2.0% in eyes without prior IOI in either dataset [4]), female sex, switching from another anti-VEGF agent (treatment-naive status conferred an adjusted hazard ratio of 0.51, 95% CI 0.38–0.69, in the IRIS two-year analysis [5]), and exposure during the early launch period (an adjusted hazard ratio of 0.68, 95% CI 0.53–0.86, was observed for the second year after launch compared with the first year [5]).

4. Discussion

This systematic review and meta-analysis of ten contemporary datasets comprising 33,280 brolucizumab-treated eyes (characteristics summarized in Table 1) estimated the pooled cumulative incidence of any IOI, RV, or RVO event after intravitreal brolucizumab 6 mg in eyes with neovascular age-related macular degeneration at 5.54% (95% CI 4.23–7.02%; 95% prediction interval approximately 3.1–8.6%; Figure 3). The estimate was substantially heterogeneous (I^2 = 94.0%) and was markedly higher in randomized or prospective studies with independent safety adjudication (8.42%) than in retrospective or registry cohorts relying on chart-review or claims coding (4.35%; Table 2). The estimate was robust in leave-one-out sensitivity analysis, in alternative-estimator sensitivity analyses, and in the GLMM. Significant funnel-plot asymmetry was identified by both Egger's and Peters' tests (Figure 4), but trim-and-fill imputation indicated that the adjusted estimate (5.21%) would not differ substantively from the unadjusted estimate of 5.54%. Component-level estimates indicated that isolated RV occurred in 0.6–3.3% of treated eyes (unweighted mean 1.6%) and RVO in 0.4–2.2% (unweighted mean 1.5%), with isolated IOI representing the majority of the composite numerator.

The pooled estimate is closely consistent with the independently adjudicated rate originally reported by the Safety Review Committee of the HAWK and HARRIER trials, in which the cumulative incidence of definite or probable inflammatory events was 4.6% [2]. It is somewhat lower than the approximately 10–11% reported in the OCTOPUS and SWIFT phase IIIb studies [6] and the MERLIN trial of monthly dosing [9], and it sits between the lower bound of approximately

2.4% reported in the Komodo Healthcare Map claims analysis [4] and the upper bound of approximately 8.4% in the Japanese PHEASANT cohort [7]. The early single-centre series of Enríquez and colleagues reported intraocular inflammation in 8.1% of 172 eyes, with one case of occlusive retinal vasculitis [21], which is consistent with the present synthesis. Earlier expert reviews and consensus statements [3,8] drew attention to the variability of reported rates but did not provide a single pooled quantitative estimate. To the best of the present authors' knowledge, this is the first comprehensive meta-analytic synthesis to integrate the pivotal trials, the phase IIIb prospective studies, the two major United States real-world data sources, and four geographically diverse cohorts from North America, Europe, and Asia under a single methodological framework. The synthesis is also consistent with the safety experience reported in the KESTREL and KITE phase 3 trials of brolucizumab in diabetic macular edema [22,23], in which intraocular inflammation rates were 4.2% and 2.2% respectively, with isolated retinal vasculitis at 0.5% or below; this concordance across indications supports the view that the inflammatory signal is intrinsic to brolucizumab and not unique to nAMD eyes.

To inform clinical positioning, it is helpful to compare the present pooled estimate with the corresponding rates for the principal alternative anti-VEGF agents. In the HAWK and HARRIER trials [1,2], the comparator aflibercept 2 mg every 8 weeks produced an IOI rate of 1.1% with no occlusive vasculitis. In the TENAYA and LUCERNE phase 3 trials of faricimab in nAMD [24], overall ocular adverse event rates were comparable between faricimab and aflibercept (36.3% versus 38.1% in TENAYA, and 40.2% versus 36.2% in LUCERNE), with rates of intraocular inflammation specifically substantially lower than the present pooled estimate for brolucizumab. In the PULSAR phase 3 trial of high-dose aflibercept 8 mg [25], the incidence of any ocular adverse event in the study eye was 38–39% across treatment arms and was similar to aflibercept 2 mg, again with low specific IOI rates. Against this background, the present pooled estimate of 5.54% for brolucizumab 6 mg (Figure 3) appears severalfold higher than for the principal alternative agents. This comparison must, however, be interpreted in the context of the durability advantage offered by brolucizumab, which may be clinically meaningful for individual patients who would otherwise require monthly injections.

The clinical entity of brolucizumab-associated occlusive retinal vasculitis is widely thought to be immune-mediated. The leading mechanistic hypotheses include the formation of anti-drug antibodies that may cross-react with retinal vascular endothelial antigens, the deposition of immune complexes within the retinal vasculature, the role of the unusually high molar concentration of brolucizumab achievable in the eye, and a possible contribution from vehicle components or container leachables including silicone oil [8]. These hypotheses are supported by the temporal clustering of events within the first few months within the first few months and within the loading phase [5,6,12], and with the association observed in the IRIS Registry analyses between a prior history of intraocular inflammation and an approximately four- to five-fold higher observed risk of subsequent events [4,5]. The descriptive observation that male sex, older age, and treatment-naive status were associated with a lower risk in the IRIS Registry two-year analysis [5] remains to be mechanistically explained, but may reflect either residual confounding by indication or differences in the immune environment of switched versus naive eyes. The role of HLA typing in determining susceptibility has been postulated but has not been adequately studied; this represents a priority area for future biomarker research. The practical implication of these observations for patient selection is that brolucizumab should generally be avoided in eyes with a documented history of intraocular inflammation in the preceding twelve months, and that the threshold for switching to brolucizumab in patients with multiple risk factors should be high.

The substantial heterogeneity observed in this meta-analysis (I^2 of 94.0% and visible in Figure 3) is best understood as reflecting the diversity of study designs and data sources rather than as random sampling variability. Three sources are particularly important. First, ascertainment methods differed markedly, ranging from prospective image-based adjudication by an independent Safety Review

Committee at all study visits in the pivotal trials [2,9], through systematic adverse event reporting in phase IIIb single-arm studies [6], to retrospective ICD coding in claims-based registries [4,5]. The HAWK and HARRIER Safety Review Committee analysis [2] reclassified many investigator-reported cases and is widely regarded as the most sensitive available estimate; the very large registry analyses [4,5] are likely to underestimate true incidence because asymptomatic or mild inflammation is undercaptured in coding data. Second, follow-up duration varied from a median of approximately three months in the Komodo Healthcare Map analysis [4] to twenty-four months in the IRIS two-year and MERLIN two-year reports [5,9], as documented in Table 1. Because most inflammatory events occur within six months, the longer-follow-up analyses approach the asymptotic cumulative incidence more closely, whereas shorter analyses systematically underestimate it. Third, treatment intensity differed: the MERLIN trial [9] deliberately tested fixed monthly dosing in eyes with recalcitrant disease and produced a numerically higher event rate than the originally licensed every-eight-week to every-twelve-week dosing, while real-world cohorts predominantly used label-conforming intervals. The meta-regression analysis indicated that log sample size was negatively associated with the log-odds of the event ($\beta = -0.78$; $p = 0.054$), consistent with a small-study effect that mirrors the funnel-plot asymmetry shown in Figure 4.

For clinicians, the findings of this synthesis support the practice of careful patient selection, comprehensive baseline screening including dilated fundoscopy and (where available) widefield fluorescein angiography, and the documentation of any prior history of intraocular inflammation. Patients should be educated to report promptly the onset of floaters, blurred vision, or any new symptoms suggestive of inflammation, particularly during the first six months of treatment when the great majority of events occur. When symptoms develop, prompt fundus photography, optical coherence tomography, and fluorescein angiography with peripheral sweeps are recommended[3,8]. Brolucizumab should be discontinued and intensive corticosteroid therapy (topical, periocular, intravitreal, or systemic, depending on severity) initiated at the earliest sign of intraocular inflammation[3,8]. The findings also support a measured approach to the position of brolucizumab among newer agents. For the Indonesian context, where retinal services are concentrated in tertiary centres and many patients travel substantial distances for follow-up, the durability advantage of brolucizumab in reducing injection frequency is potentially valuable; however, the elevated inflammatory risk must be communicated clearly to patients and balanced against the alternative of more frequent injections of aflibercept 2 mg, faricimab[24], or aflibercept 8 mg[25,26]. Centres of excellence such as Bali Mandara Regional General Hospital have a particular responsibility to develop locally-adapted standard operating procedures for baseline screening, patient education, and the recognition and management of brolucizumab-associated inflammatory events, drawing on the international evidence summarized in Table 1 and on regional experience.

This meta-analysis has several limitations that should be considered when interpreting the findings. First, all included studies were observational with respect to the safety outcome of interest (the randomized trials [2,9] provided post-hoc safety subset analyses rather than primary safety endpoints), and residual confounding by indication is likely to influence the registry estimates[4,5], because brolucizumab was preferentially used in eyes that had previously demonstrated incomplete response to other anti-VEGF agents. Second, between-study heterogeneity was substantial (I^2 94.0%; Figure 3), and although heterogeneity was partially explained by the design subgroup analysis (Table 2) and the meta-regression, the pooled estimate should be interpreted as a summary of the available evidence rather than as a single 'true' incidence figure applicable to every clinical context. Third, the definitions of IOI, RV, and RVO varied across studies, and several reports combined these into composite outcomes without separately reporting each component; the component-level estimates should therefore be interpreted as approximate. Fourth, the funnel-plot asymmetry detected in Figure 4 raises the possibility of small-study effects or selective publication. Fifth, all ten of the included studies (Table 1) received funding or

industry co-authorship from the marketing authorisation holder, which introduces the possibility of sponsorship-related reporting effects; however, the registry analyses provided lower estimates than the prospective studies, which is contrary to what would be expected from such a bias. Sixth, the meta-analysis was limited to English-language publications and to indexed peer-reviewed journals. Seventh, the synthesis was based on aggregate study-level data, and individual patient data meta-analysis would have permitted more refined adjustment for prior anti-VEGF history, age, sex, and other potential modifiers. Eighth, long-term outcomes data beyond two years are not yet available; the temporal clustering of events within the first six months is reassuring, but the available evidence does not exclude a long tail of later events.

Future research should focus on several priorities. First, prospective ascertainment of immunological correlates of inflammatory events, including anti-drug antibody titres, HLA typing, and complement profiling, may help to identify patients at greater risk before treatment. Second, head-to-head comparative real-world studies of brolucizumab and newer agents (faricimab [24] and aflibercept 8 mg [25]) are needed, using consistent definitions and adjudication procedures to support evidence-based positioning. Third, longer-term follow-up of the existing registry cohorts [4,5] is required to determine whether the temporal clustering of events within the first six months represents a true window of vulnerability or a surveillance artifact. Fourth, individual patient data meta-analyses incorporating the IRIS Registry, the Komodo Healthcare Map, the FRB Spain database [13], and the Japanese PHEASANT cohort [7] would substantially refine risk stratification.

5. Conclusion

In this systematic review and meta-analysis of ten contemporary datasets (Table 1) encompassing 33,280 eyes with neovascular age-related macular degeneration treated with intravitreal brolucizumab 6 mg, the pooled cumulative incidence of any intraocular inflammation, retinal vasculitis, or retinal vascular occlusion event was estimated at 5.54% (95% CI 4.23–7.02%; 95% prediction interval approximately 3.1–8.6%; Figure 3). The estimate was substantially heterogeneous (I^2 94.0%, Cochran's Q 150.48, $p < 0.0001$), and the heterogeneity was partially explained by study design, with randomized controlled trials and phase IIIb prospective studies using independent Safety Review Committee adjudication reporting a higher pooled incidence (8.42%, 95% CI 4.12–14.04%) than retrospective and registry cohorts relying on chart-review or claims coding (4.35%, 95% CI 3.28–5.56%; Table 2). The pooled estimate was robust in leave-one-out sensitivity analysis (4.98–6.19%), in alternative-estimator sensitivity analyses using restricted maximum likelihood and Paule–Mandel approaches, and in a generalised linear mixed model with logit link. Significant funnel-plot asymmetry was detected by both Egger's and Peters' tests (Figure 4; $p = 0.011$ and 0.029 respectively), but the trim-and-fill adjusted estimate of 5.21% did not differ substantively from the unadjusted estimate. Component-level estimates indicated isolated retinal vasculitis in 0.6–3.3% and retinal vascular occlusion in 0.4–2.2% of treated eyes, with isolated intraocular inflammation accounting for the majority of the composite numerator. More than three-quarters of inflammatory events occurred within six months of the first brolucizumab injection, and severe vision loss of at least 15 ETDRS letters was reported in 0.74% of treated eyes in the pivotal trials and in 6.2% of eyes in the MERLIN study.

Identified risk factors for events included a prior history of intraocular inflammation in the twelve months preceding brolucizumab initiation, female sex, switching from another anti-VEGF agent, and exposure during the early launch period. Comparative inflammatory event rates for aflibercept 2 mg, faricimab, and high-dose aflibercept 8 mg are substantially lower than the present pooled estimate for brolucizumab 6 mg, although this comparison must be balanced against the durability advantage of brolucizumab in selected patients. These findings, which are restricted to the 6 mg dose and to the nAMD indication, support continued pharmacovigilance for brolucizumab-associated inflammatory complications and reinforce the importance of careful patient selection (with avoidance of eyes with recent intraocular inflammation), comprehensive baseline screening, structured patient education regarding

early symptoms, and intensified monitoring during the first six months after treatment initiation. Where an inflammatory event is recognised, prompt cessation of brolucizumab and the timely initiation of intensive corticosteroid therapy are warranted. The present synthesis offers clinicians and policy-makers a quantitatively defensible estimate against which the durability advantages and the risk profile of brolucizumab can be balanced for individual patients with neovascular age-related macular degeneration in routine ophthalmic practice in Indonesia and globally.

6. References

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