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Review Article

Effectiveness of ocriplasmin in real-world settings: A systematic literature review, meta-analysis, and comparison with randomized trials

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ABSTRACT.

Purpose.
Effectiveness of ocriplasmin for vitreomacular traction (VMT) varies depending on the presence of common ocular conditions and patient selection criteria. We carried out a systematic literature review and meta-analysis of ocriplasmin studies conducted in real-world settings (RWS) and compared outcomes with those from randomized controlled trials (RCTs).

Methods.
We included prospective and retrospective studies from RWS documenting effectiveness of ocriplasmin in patients with VMT with or without MH, and RCTs of ocriplasmin versus control. Key end-points were vitreomacular adhesion resolution (VMAR), nonsurgical MH closure, need for vitrectomy and safety. We conducted meta-regression on pooled results to evaluate effects of baseline covariates and study design on outcomes.

Results.
Thirty RWS (2402 patients) and 5 RCTs (737 patients) were included epiretinal membrane (ERM) and broad VMA were more prevalent in RCTs. Primary VMAR, vitrectomy and MH closure rates were comparable between RWS and RCTs. Rates of nsVMAR were significantly higher in RWS than RCTs (odds ratio 1.66; 95% confidence interval [CI]: 1.18–2.34). nsVMAR rates were inversely associated with ERM prevalence (odds ratio 0.20; 95% CI: 0.08–0.51). Compared with the recent OASIS trial, RWS reported a higher incidence of new/worsening subretinal fluid cases and less photophobia, photopsia, vitreous floaters, electroretinogram abnormalities and MH progression.

Conclusions.
Ocriplasmin was significantly more effective in achieving nsVMAR in RWS than in RCTs. Lower ERM prevalence in RWS was the single significant explanatory variable for this difference. Conclusions on ocriplasmin safety in RWS are limited due to inconsistent reporting.

Key words: Ocriplasmin – vitreomacular traction – effectiveness – real world

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Introduction

The human vitreous is a clear, gel-like structure that consists of primarily of water (98%), collagen and hyaluronan. Over decades during midlife, the vitreous liquefies while it progressively separates from the posterior vitreous cortex, eventually leading to full posterior vitreoretinal detachment (PVD) (Sebag 2009; Duker et al. 2013). In rare cases, this process does not complete, and the vitreous remains attached, mostly in areas where the vitreoretinal interface is strongest, including the vitreous base, the large retinal vessels, the optic disc margin and the 500-μm diameter foveola (Johnson 2010). The tractional effects of incomplete PVD can result in deformities at the level of the fovea, giving rise to metamorphopsia, blurring and decreased visual acuity (Ezra 2001; Johnson 2010). Continued traction may lead to the development of epiretinal membrane (ERM) (Joshi et al. 2013) or full-thickness macular hole (MH) (Ezra 2001).

Ocriplasmin (JETREA, Oxurion, Leuven, Belgium) is a truncated, recombinant form of human plasmin that has proteolytic activity against protein components of the vitreous body and the vitreoretinal interface such as laminin, fibronectin and collagen (European Medicines Agency 2013). Ocriplasmin is approved for the treatment of symptomatic

vitreomacular adhesion (VMA)/vitreomacular traction (collectively: 'VMT') with or without macular hole (MH) ≤400 μm. Some authors have characterized its efficacy as modest (European Medicines Agency 2013; Jackson et al. 2013; Kim et al. 2013; Lim et al. 2017). However, post hoc analyses of these trials have shown that several ocular and patient characteristics, including presence of ERM, broad VMA adhesion size (>1500 μm), older age\, and non-phakic lens status, were associated with lower rates of VMA resolution (VMAR), while larger MHs (>250 μm) were associated with lower closure rates (Haller et al. 2015; Jackson et al. 2016). We hypothesized that careful patient selection based on these risk factors may increase the effectiveness of ocriplasmin in real-world settings (Khanani et al. 2019). We conducted a systematic literature review and meta-analysis of ocriplasmin use in clinical practice to evaluate the effectiveness of a single 125-μg dose in patients with symptomatic VMA or VMT with or without MH in real-world settings (RWS). We compared our findings with results from randomized controlled trials (RCTs), which we identified through a separate systematic literature review.

Materials and methods

Eligibility criteria for considering studies for this review

We performed two separate systematic literature searches. First, we included prospective or retrospective studies documenting the effectiveness of single doses of ocriplasmin (125 μg) in the treatment of adult patients with VMT with or without MH who had received treatment in RWS. The second literature search identified double-blind RCTs using single-dose (125 μg) ocriplasmin versus control in the treatment of adults with VMT/symptomatic VMA. The main end-point was the incidence of VMAR, which we reported as primary VMAR (pVMAR, defined as VMAR occurring after ocriplasmin injection, regardless of subsequent events), and nonsurgical VMAR (nsVMAR, defined as VMAR without the need for subsequent vitrectomy). Secondary end-points were nonsurgical MH closure, the need for vitrectomy, and safety. To qualify for inclusion, studies had to report either pVMAR or nsVMAR outcomes and have a mean follow-up of at least 4 weeks after injection.

Search methods for identifying studies

To identify publications of ocriplasmin use in RWS, we searched PubMed (National Institutes of Health) and EMBASE (Elsevier) using general terms describing VMT, combined with the term 'ocriplasmin' or 'Jetrea' without any time period restriction (see Table S1 for EMBASE search terms). We excluded RCTs, safety-only reports, conference abstracts and series smaller than 12 patients. We did not contact authors for further information.

To identify RCTs, we searched EMBASE, PubMed and the Cochrane CENTRAL database for articles with ocriplasmin as a major topic and applied search filters without any time period restriction (Robinson & Dickersin 2002; Wong et al. 2006). Table S2 lists the EMBASE search terms for this search. We excluded conference abstracts and series smaller than 12 patients. Oxurion provided the clinical study databases for the identified trials.

The RWS and RCT searches were first executed on 28 October 2018 and 04 January 2019, respectively, and were updated on 5 June 2019; no new studies were found. We used EndNote X8 to collate the records from the respective literature searches and remove duplicates. We used the Covidence web app (Covidence, Melbourne, Australia) to review records and assign eligibility status.

Study selection

Two investigators (authors KHB, BL) independently reviewed title, abstract and full text. Discrepancies were resolved by discussion.

Data collection and risk of bias assessment

Data from included RWS were extracted by KHB into a Microsoft Excel spreadsheet and independently verified by BL. KHB checked all suggested corrections against the full text. Discordant readouts were resolved by discussion. For RWS, we extracted average study follow-up and clinically relevant baseline characteristics including the number of patients/treated eyes, age, sex, MH status, ERM prevalence, focal VMA, lens status and best-corrected visual acuity (BCVA). We extracted data on nonsurgical and primary VMAR, overall vitrectomy, vitrectomy after successful pVMAR, MH closure, and ≥10 Early Treatment Diabetic Retinopathy Study (ETDRS) letter gain in BCVA for the overall population and by MH status, as applicable.

Safety end-points included the incidence of retinal breaks/detachment, dyschromatopsia, new or worsening electroretinogram (ERG), subretinal fluid (SRF) and ellipsoid zone (EZ) abnormalities, MH progression, BCVA loss of ≥10 ETDRS letters and lens subluxation. If publications contained discrepancies in results presented in text or in tables, results from tables were upheld. KHB and BL independently assessed studies using the Quality Assessment Tool for Case Series Studies (National Heart, Lung and Blood Institute, Bethesda, MD) (National Heart Lung & Blood Institute 2019). Discrepant evaluations were resolved by discussion. Details on the study selection process and quality assessment for the RWS, and the full Risk of Bias spreadsheet for the RCTs are provided in Supplemental files 1, 2 and 3, respectively.

For the RCTs, we converted the original study databases into Stata data sets. KHB evaluated risk of bias using the Cochrane Risk of Bias Tool 2 (Higgins et al. 2016), using clinical study protocols, clinical study reports and statistical analysis plans. Dr Timothy Jackson independently reviewed the resulting output, and Dr Jackson's amendments were integrated into the final output.

Data synthesis and analysis

Our analysis used all treated eyes as the denominator. We evaluated effectiveness overall and separately for eyes with MH (MH group) and eyes with VMT without MH (VMT group). If outcomes were reported for more than one time-point, those from the last observation time-point were deemed most relevant and were included in the analysis. For the RCTs, we chose Month 6 as the relevant evaluation time-point for comparison with the RWS.

We analysed all data in Stata 16.0. Missing means and standard deviations (SD) of baseline characteristics were imputed using the method by Hozo et al (Hozo et al. 2005). The dichotomous treatment effectiveness estimates were calculated using a mixed effects logistic regression model with study as random effect and reported as proportions with their 95% confidence intervals. Forest plots show exact confidence intervals for individual study estimates and Wald confidence intervals for pooled estimates. Between-study heterogeneity was assessed by the χ^2 statistic of the likelihood ratio (LR) test comparing the random and fixed effects model (Nyaga et al. 2014).

We conducted a mixed effects meta-regression to assess the prognostic value of study-level covariates on pVMAR, nsVMAR and vitrectomy. Study was included as random effect, while study design (RCT = 0, RWS = 1), age (years), length of follow-up (months) and within-study proportions of ERM, MH, pseudophakia and women were included as fixed effects. Covariates were initially tested one by one, and those that were significant at the 0.05 level in the univariate analysis were included in a multivariate model. Funnel plots were used to evaluate the risk of publication bias among the studies. All statistical tests were two-sided.

The RCT systematic review protocol is registered with PROSPERO (CRD42019121138). It was not possible to register the RWS review because data extraction had already started when registration was attempted (a new PROSPERO rule that went into effect in January 2019).

Results

Study population

For the RWS (Fig. 1, Panel A), we identified 392 records, 117 of which were duplicates. We screened the titles and abstracts of 275 publications and assessed the full text for 47 publications. At this stage of our analysis, we excluded 17 studies; 6 of these exclusions were due to part or all of the data being included in a later, collaborative paper (Paul et al. 2018). We retained 30 publications (2402 patients, 2416 eyes) for analysis.

For the RCTs (Fig. 1, Panel B), 335 potentially eligible records were identified. After removing duplicates, 215 were screened at the title and abstract level. Full text was assessed for 31 records. In total, 15 publications were included, which described 5 unique RCTs, all sponsored by Oxurion, the manufacturer of ocriplasmin. These included the dose-ranging Microplasmin for Intravenous Injection (MIVI) IIT trial (NCT00435539), the pivotal Microplasmin for Intravitreous Injection-Traction Release without Surgical Treatment (MIVI-TRUST) trials MIVI 006 (NCT00781859) and MIVI 007 (NCT00798317), and the long-term Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) trial (NCT01429441). A fifth trial (NCT01889251) codenamed J-12-075 was conducted in Japan and had not been published as of March 2019. Oxurion made individual participant data available for all 5 trials.

Table 1 summarizes the design and patient baseline characteristics for each study. Mean age was 70.8 (standard deviation [SD] 3.59) years, 1439 participants (68.1%) were women, and 600 (25.0%) presented with MH at baseline. Most RWS were single-centre retrospective series with 21 (70%) having fewer than 50 patients. Two studies only included patients with MH while 3 studies included only patients with

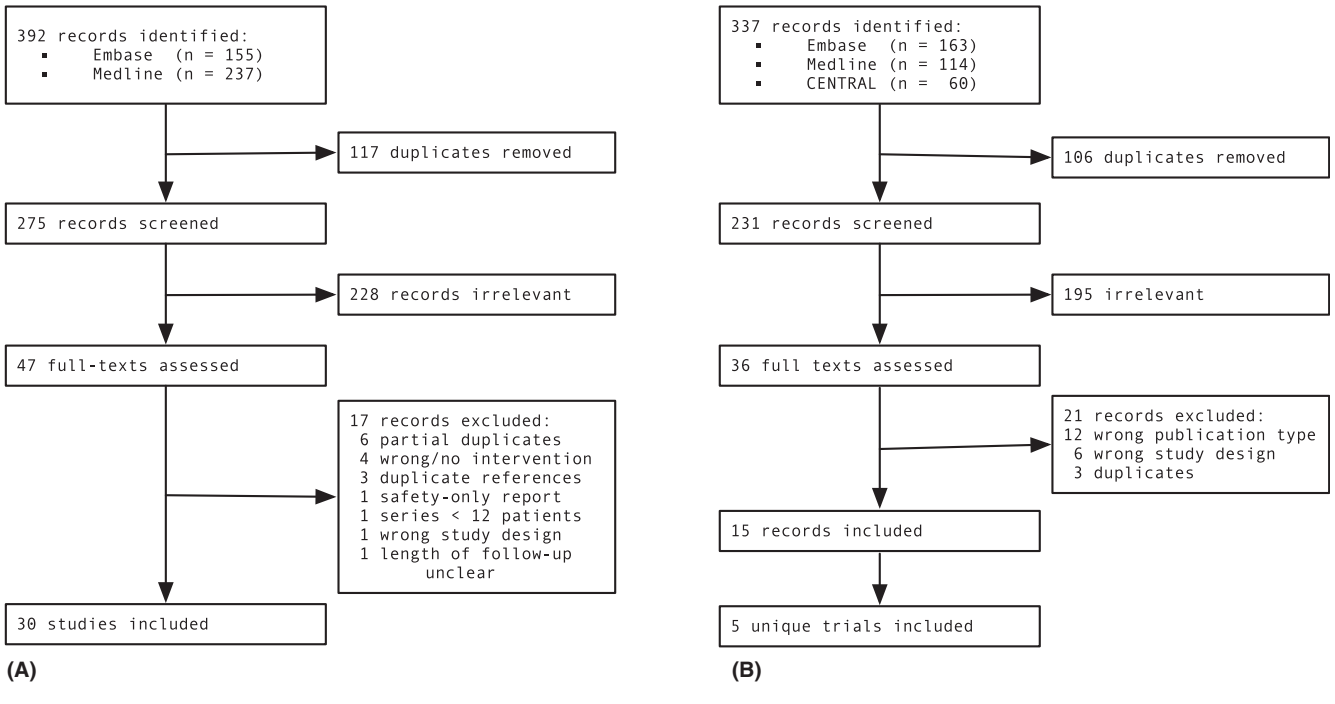

Fig. 1. PRISMA flow chart for (A) real-world studies and (B) randomized controlled trials. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Patient baseline characteristics of included real-world studies

Author (year)	Design	Patients	Age, mean (SD)	Women, N (%)	Eyes	MH, N (%)	ERM, N (%)	Focal VMA, N (%)	Phakic, N (%)	Baseline logMAR, mean (SD)	Follow-up (weeks), mean (SD)
(Barca et al. 2018)	R	74	71.0	46 (62.2)	74	20 (27.0)	12 (16.2)	71 (95.9)	61 (82.4)	0.48 (0.31)	16 (9)
(Cacciamani et al. 2017)	P	15	55.1 (4.6)	9 (60.0)	16	0 (0.0)	0 (0.0)	16 (100.0)	12 (75.0)	0.12	26 (0)
(Cereda et al. 2017)	R	15	70.0	10 (66.7)	15	5 (33.3)	0 (0.0)	15 (100.0)	15 (100.0)	0.40	26 (0)
(Chatziralli et al. 2016c)	P	24	71.4 (8.7)	16 (66.7)	24	7 (29.2)	3 (12.5)	24 (100.0)	15 (62.5)	0.28 (0.24)	8 (3)
(Feng et al. 2018)	R	47	71.0 (10.0)	33 (70.2)	49	16 (32.7)	12 (24.5)	43 (87.8)	32 (65.3)	0.64 (0.28)	45 (9)
(Figueira et al. 2016)	R	78	70.9 (8.7)	54 (69.2)	83	12 (14.5)	9 (10.8)	83 (100.0)	60 (72.3)	0.40	20 (17)
(Haynes et al. 2017)	R	241	.		241	112 (46.5)				.	.
(Heider et al. 2016)	R	96	70.8 (9.2)	55 (57.3)	96	5 (5.2)	16 (16.7)	78 (81.2)	62 (64.6)	0.37 (0.21)	31 (28)
(Itoh et al. 2014)	R	19	69.6	14 (73.7)	19				12 (63.2)	0.30	12 (0)
(Khanani et al. 2019)	P	539	71.1 (8.3)	345 (64.0)	539	137 (25.4)	129 (23.9)	449 (83.3)	359 (66.6)	.	32 (16)
(Kim et al. 2013)	R	19	71.2 (6.4)	11 (57.9)	19	6 (31.6)	8 (42.1)	16 (84.2)	15 (78.9)	0.44 (0.21)	8 (5)
(Lenk et al. 2018)	R	21	71.1 (10.7)	14 (66.7)	23	4 (17.4)	1 (4.3)	23 (100.0)	16 (69.6)	0.39 (0.25)	.
(Lim et al. 2017)	R	208	.	143 (68.8)	208	75 (36.1)		179 (86.1)		0.52 (0.34)	29
(Manousaridis et al., 2017)	R	20	68.5		20	6 (30.0)	1 (5.0)	20 (100.0)		0.51	4
(Mastropasqua et al. 2016)	R	14	.	11 (78.6)	14	0 (0.0)	4 (28.6)		13 (92.9)	0.33 (0.24)	4 (0)
(Meyer et al. 2015)	R	22	72.4 (10.2)	14 (63.6)	22	3 (13.6)	4 (18.2)		13 (59.1)	0.51	11 (6)
(Michalska-Malecka et al. 2016)	R	16	75.6 (6.0)		16	4 (25.0)			10 (62.5)	0.39 (0.15)	4 (0)
(Muqit et al. 2018)	R	25	71.0	17 (68.0)	25	6 (24.0)	0 (0.0)	25 (100.0)	21 (84.0)	0.52	28 (6)
(Nudleman et al. 2016)	R	35	74.1	25 (71.4)	36	9 (25.0)	12 (33.3)		17 (47.2)	0.49	51 (6)
(Paul et al. 2018)	R	167	72.7 (8.9)	118 (70.7)	167	0 (0.0)	40 (24.0)		111 (66.5)	.	.
(Quezada-Ruiz et al. 2015)	R	25	74.0	17 (68.0)	25	8 (32.0)	2 (8.0)	24 (96.0)	14 (56.0)	0.50	25 (10)
(Scholz et al. 2017)	R	14	73.0 (10.0)	12 (85.7)	14	1 (7.1)		14 (100.0)	11 (78.6)	0.36 (0.22)	13
(Sharma et al. 2015)	R	56	72.0	38 (67.9)	58	15 (25.9)	23 (39.7)	58 (100.0)	37 (63.8)	0.51 (0.37)	37 (21)
(Singh et al. 2014)	R	17	68.8 (9.0)	11 (64.7)	17	3 (17.6)	3 (17.6)	13 (76.5)	12 (70.6)	0.36	.
(Steel et al. 2015)	P	12	72.6 (4.0)	9 (75.0)	12	12 (100.0)	2 (16.7)	12 (100.0)	10 (83.3)	.	12 (0)
(Steel et al. 2016)	R	33	71.0 (6.0)	22 (66.7)	33	31 (93.9)	0 (0.0)	31 (93.9)	26 (78.8)	0.72 (0.22)	.
(Tadayoni et al. 2018)	P	466	71.7 (8.3)	344 (73.8)	466	86 (18.5)	0 (0.0)	466 (100.0)		0.29	26
(Tschuppert & Gerding 2016)	R	12	.		12	1 (8.3)			8 (66.7)	.	.
(Warrow et al. 2015)	R	35	69.4 (9.2)	23 (65.7)	35	6 (17.1)	6 (17.1)	33 (94.3)	25 (71.4)	0.46 (0.35)	14 (7)
(Willekens et al. 2015)	R	37	71.2 (9.5)	28 (75.7)	38	10 (26.3)	2 (5.3)	37 (97.4)	32 (84.2)	.	.
Summary[a]		2402	70.8 (3.59)	1439 (68.1)	2416	600 (25.0)	289 (15.2)	1730 (91.6)	1019 (68.8)	0.43 (0.13)	20.9 (12.99)

ERM = epiretinal membrane; logMAR = logarithm of the minimal angle of resolution; MH = macular hole; P = prospective; R = retrospective; SD = standard deviation; VMA = vitreomacular adhesion.

[a] Percentages in this row refer to the proportion of patients with a given characteristic (e.g. MH) among the studies that reported this characteristic.

Table 2. Baseline characteristics of ocriplasmin-treated patients in randomized controlled trials.

Trial	Patients	Age (years), mean (SD)	Women, N (%)	MH, N (%)	ERM, N (%)	Focal VMA, N (%)	Phakic, N (%)	Baseline logMAR, mean (SD)	Follow-up (weeks)
MIVI IIT (Stalmans et al. 2010)	13	74.2 (5.7)	8 (61.5)	1 (7.7)	N/A	N/A	7 (53.8)	0.51 (0.20)	26
MIVI 006 (Stalmans et al. 2012)	219	71.5 (10.2)	148 (67.6)	57 (26.0)	86 (39.3)	145 (66.2)	128 (58.4)	0.41 (0.22)	26
MIVI 007 (Stalmans et al. 2012)	245	72.6 (7.6)	166 (67.8)	49 (20.0)	98 (40.0)	169 (69.0)	164 (66.9)	0.43 (0.27)	26
OASIS (Dugel et al. 2016)	145	69.4 (10.0)	102 (70.3)	50 (34.5)	33 (22.8)	128 (88.3)	106 (73.1)	0.43 (0.18)	104
J-12-075[a]	115	68.1 (7.3)	59 (51.3)	43 (37.4)	35 (30.4)	104 (90.4)	104 (90.4)	0.39 (0.18)	26
Summary	737	70.6 (9.44)	483 (65.5)	200 (27.1)	252 (34.2)	546 (74.1)	509 (69.1)	0.42 (0.23)	

For all percentages shown in the table, the denominator is number of patients; this is the same as number of eyes for all RCTs.
ERM = epiretinal membrane; logMAR = logarithm of the minimal angle of resolution; MH = macular hole; MIVI = Microplasmin for Intravenous Injection; MIVI-TRUST = Microplasmin for Intravitreous Injection-Traction Release without Surgical Treatment; N/A = not assessed; OASIS = Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole; SD = standard deviation; VMA = vitreomacular adhesion.
[a] Study J-12-075 (NCT01889251) has not been published to date.

VMT. Five studies were prospective in nature, including two Oxurion-sponsored observational studies (Tadayoni et al. 2018; Khanani et al. 2019).

Epiretinal membranes, reported in 23 studies, were present in 289 patients (15.2%). Mean weighted BCVA (24 studies) was 0.43 logMAR (63.5 ETDRS letters). Average follow-up was reported for 23 studies and ranged from 4 to 52 weeks (unweighted average: 20.9 weeks). Minimum follow-up (reported in 23 studies) ranged from 1 to 52 weeks.

Reporting quality of treatment outcomes in RWS was variable and often incomplete. The quality assessment grid (Fig. S1) indicates that lack of information on statistical methodology and incompleteness of reporting (for the purpose of our analysis) were the most common deficiencies.

Patient baseline characteristics of the ocriplasmin RCTs are described in Table 2. Mean age and BCVA were comparable to those of the RWS, as were the proportions of women, phakic eyes and eyes with MH. On the other hand, the proportion of ERM was twofold greater than in the RWS, while focal VMA was less frequent than in the RWS.

Overall risk of bias in the RCTs was low (Fig. S2). The MIVI 006 and MIVI 007 trials were placebo-controlled, while the other trials used sham injection as control, administered by a trial site member who did not participate in the evaluation of patients. All outcomes were prespecified, intention-to-treat analysis was used throughout, and missing values were imputed using the 'last observation carried forward' method.

Effectiveness in RWS

Table 3 shows the VMAR, vitrectomy and MH closure outcomes by study. While only 2 publications explicitly reported nsVMAR outcomes (Lim et al. 2017; Tadayoni et al. 2018), 13 more studies contained sufficient information to derive nsVMAR outcomes. Nonsurgical VMAR rates were therefore available for 15 studies, 14 of which detailed outcomes in VMT patients and 14 in MH patients. Six studies did not report separate VMAR incidence rates for the VMT and MH subgroups, and 8 studies did not report the incidence of vitrectomy.

Figures 3 and 4 show the random effect forest plots of VMAR outcomes in VMT and MH patients, respectively. Among VMAR outcomes, pVMAR was most commonly reported. For the overall population, its pooled estimate of 51.8% (95% CI: 49.6% to 54.0%; 28 studies, 1967 eyes) was approximately 7% higher than the nsVMAR estimate (44.5%; 95% CI: 39.7% to 49.4%; 15 studies, 1003 eyes). This difference was mostly due to the MH group, where initial (primary) VMAR success rates were reduced by 16.5% due to post-VMAR vitrectomies (Table 3, Fig. 2). Nonsurgical MH closure occurred in 35.4% of MH eyes (95% CI: 30.4% to 40.7%) – Fig. 4.

Effectiveness comparison between RWS and RCTs

We subsequently performed an analysis comparing outcomes between RWS and the 5 Oxurion-sponsored RCTs. Given the average length of follow-up observed in the RWS (20.9 weeks), we chose the 26-week evaluation timepoint of the RCTs to compare their results with the RWS.

Nonsurgical VMAR outcomes were significantly better in RWS than in RCTs (OR 1.66; 95% CI: 1.18–2.34; $p = 0.004$) while other outcomes tended to be similar (Table 4). We used meta-regression to evaluate the prognostic value of baseline covariates on the effectiveness outcomes in the pooled RWS and RCT populations. We initially limited the multivariate meta-regression to those studies that had information on all covariates that were significant in the univariate regression (results not shown). Since relatively few RWS reported all covariates of interest, this approach led to the exclusion of the majority of RWS and a preponderance of RCTs in the analyses. We therefore reran the univariate and multivariate meta-regression without this limitation. The final results (shown in Table 5) indicated that in this broader analysis, the same covariates remained significant in the multivariate meta-regression, with similar ORs. For nsVMAR, study design and proportion of ERM in the study were significant in univariate analysis, but only ERM remained significant when the two covariates were combined in a

Table 3. Main efficacy outcomes of included real-world studies.

	Nonsurgical VMAR			Primary VMAR			Vitrectomy			MH closure
Author (year)	All	VMT	MH	All	VMT	MH	All	VMT	MH	MH
(Barca et al. 2018)				44/74 (59.5)			12/74 (16.2)			8/20 (40.0)
(Cacciamani et al. 2017)	11/16 (68.8)	11/16 (68.8)		11/16 (68.8)	11/16 (68.8)		0/16 (0.0)	0/16 (0.0)		
(Cereda et al. 2017)	10/15 (66.7)	7/10 (70.0)	3/5 (60.0)	12/15 (80.0)	7/10 (70.0)	5/5 (100.0)	2/15 (13.3)	0/10 (0.0)	2/5 (40.0)	3/5 (60.0)
(Chatziralli et al. 2016c)				16/24 (66.7)						2/7 (28.6)
(Feng et al. 2018)	14/49 (28.6)	10/33 (30.3)	4/16 (25.0)	20/49 (40.8)	11/33 (33.3)	9/16 (56.2)	25/49 (51.0)	14/33 (42.4)	11/16 (68.8)	4/16 (25.0)
(Figueira et al. 2016)				47/83 (56.6)	39/71 (54.9)	8/12 (66.7)	4/83 (4.8)	0/71 (0.0)	4/12 (33.3)	6/12 (50.0)
(Haynes et al. 2017)					44/129 (34.1)					31/112 (27.7)
(Heider et al. 2016)				40/96 (41.7)			38/96 (39.6)			0/5 (0.0)
(Itoh et al. 2014)				9/19 (47.4)						
(Khanani et al. 2019)				283/539 (52.5)	198/383 (51.7)	85/137 (62.0)	137/539 (25.4)	67/383 (17.5)	70/137 (51.1)	38/137 (27.7)
(Kim et al. 2013)	7/19 (36.8)	4/13 (30.8)	3/6 (50.0)	8/19 (42.1)	4/13 (30.8)	4/6 (66.7)	12/19 (63.2)	9/13 (69.2)	3/6 (50.0)	3/6 (50.0)
(Lenk et al. 2018)	6/23 (26.1)	4/19 (21.1)	2/4 (50.0)	8/23 (34.8)	4/19 (21.1)	4/4 (100.0)	8/23 (34.8)	6/19 (31.6)	2/4 (50.0)	2/4 (50.0)
(Lim et al. 2017)	90/208 (43.3)	60/133 (45.1)	30/75 (40.0)				65/208 (31.2)	25/133 (18.8)	33/75 (44.0)	30/75 (40.0)
(Manousaridis et al., 2017)				12/20 (60.0)			5/20 (25.0)	2/14 (14.3)	3/6 (50.0)	2/6 (33.3)
(Mastropasqua et al. 2016)				7/14 (50.0)	7/14 (50.0)					
(Meyer et al. 2015)	12/22 (54.5)	9/19 (47.4)	3/3 (100.0)	14/22 (63.6)	11/19 (57.9)	3/3 (100.0)	2/22 (9.1)	2/19 (10.5)	0/3 (0.0)	1/3 (33.3)
(Michalska-Malecka et al. 2016)				12/16 (75.0)	10/12 (83.3)	2/4 (50.0)				
(Muqit et al. 2018)	14/25 (56.0)	10/19 (52.6)	4/6 (66.7)	14/25 (56.0)	10/19 (52.6)	4/6 (66.7)	2/25 (8.0)	0/19 (0.0)	2/6 (33.3)	4/6 (66.7)
(Nudleman et al. 2016)	15/36 (41.7)	7/27 (25.9)	8/9 (88.9)	15/36 (41.7)	7/27 (25.9)	8/9 (88.9)	3/36 (8.3)	2/27 (7.4)	1/9 (11.1)	7/9 (77.8)
(Paul et al. 2018)				79/167 (47.3)	79/167 (47.3)					
(Quezada-Ruiz et al. 2015)	9/25 (36.0)	7/15 (46.7)	2/8 (25.0)	11/25 (44.0)	7/15 (46.7)	4/8 (50.0)	6/25 (24.0)	0/15 (0.0)	6/8 (75.0)	2/8 (25.0)
(Scholz et al. 2017)				7/14 (50.0)	6/13 (46.2)	1/1 (100.0)				1/1 (100.0)
(Sharma et al. 2015)	27/58 (46.6)	23/43 (53.5)	4/15 (26.7)	29/58 (50.0)	23/43 (53.5)	6/15 (40.0)	10/58 (17.2)	0/43 (0.0)	10/15 (66.7)	4/15 (26.7)
(Singh et al. 2014)	8/17 (47.1)	6/14 (42.9)	2/3 (66.7)	8/17 (47.1)	6/14 (42.9)	2/3 (66.7)	1/17 (5.9)	0/14 (0.0)	1/3 (33.3)	
(Steel et al. 2015)	3/12 (25.0)		3/12 (25.0)	7/12 (58.3)		7/12 (58.3)	9/12 (75.0)		9/12 (75.0)	3/12 (25.0)
(Steel et al. 2016)				19/33 (57.6)		19/31 (61.3)				11/31 (35.5)
(Tadayoni et al. 2018)	230/466 (49.4)	184/380 (48.4)	46/86 (53.5)	240/466 (51.5)	184/380 (48.4)	56/86 (65.1)	56/466 (12.0)	25/380 (6.6)	31/86 (36.0)	36/86 (41.9)
(Tschuppert & Gerding 2016)	5/12 (41.7)	4/11 (36.4)	1/1 (100.0)	5/12 (41.7)	4/11 (36.4)	1/1 (100.0)	3/12 (25.0)	3/11 (27.3)	0/1 (0.0)	1/1 (100.0)
(Warrow et al. 2015)				15/35 (42.9)	12/29 (41.4)	3/6 (50.0)	8/35 (22.9)	3/29 (10.3)	4/6 (66.7)	1/6 (16.7)
(Willekens et al. 2015)				27/38 (71.1)	18/28 (64.3)	9/10 (90.0)	1/38 (2.6)			4/10 (40.0)
Random effects pooled estimate, % (95% CI)	44.5 (39.7, 49.4)	44.5 (38.3, 50.7)	47.5 (35.6, 59.6)	51.8 (49.6, 54.0)	47.3 (42.4, 52.3)	64.0 (59.0, 68.7)	19.1 (12.7, 27.6)	6.9 (2.7, 16.6)	47.6 (39.8, 55.4)	35.4 (30.4, 40.7)

CI = confidence interval; MH = macular hole; SD = standard deviation; VMAR = vitreomacular adhesion resolution; VMT = vitreomacular traction.

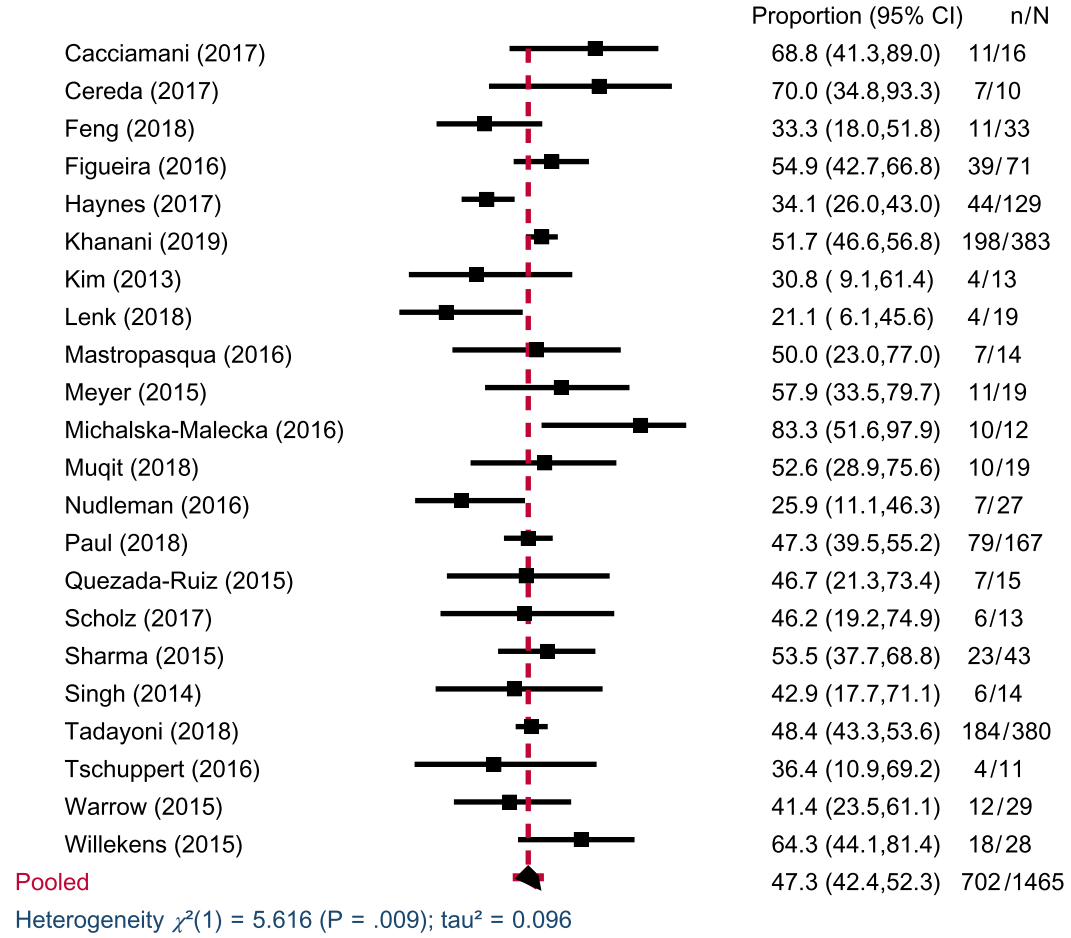

Fig. 2. Incidence of primary (A) and nonsurgical VMA (B) resolution in patients with VMT, in real-world settings. CI = confidence interval; VMA = vitreomacular adhesion; VMAR = vitreomacular adhesion resolution.

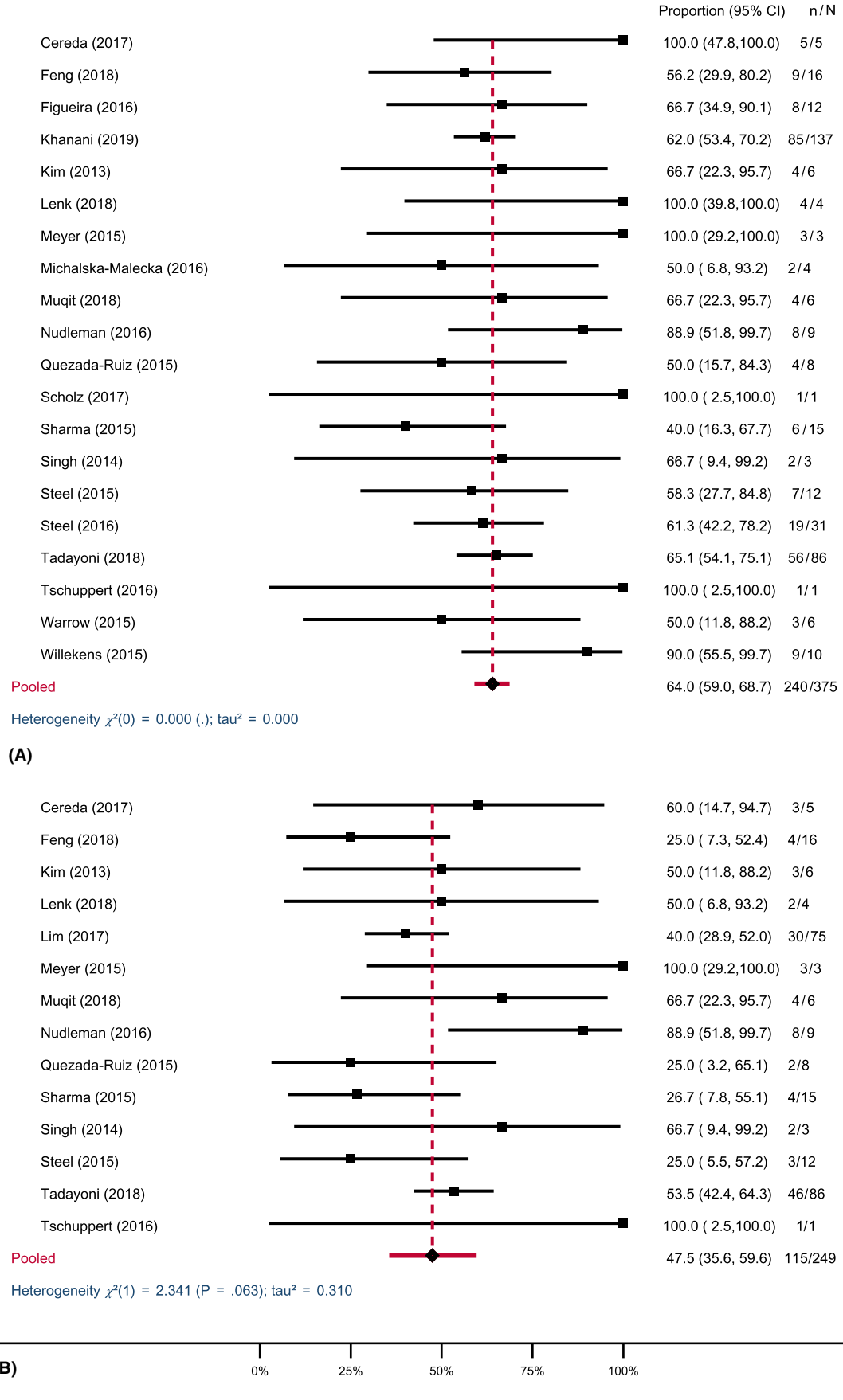

Fig. 3. Incidence of primary (A) and nonsurgical (B) VMA resolution in patients with MH, in real-world settings. CI = confidence interval; MH = macular hole; VMA = vitreomacular adhesion; VMAR = vitreomacular adhesion resolution; VMT = vitreomacular traction.

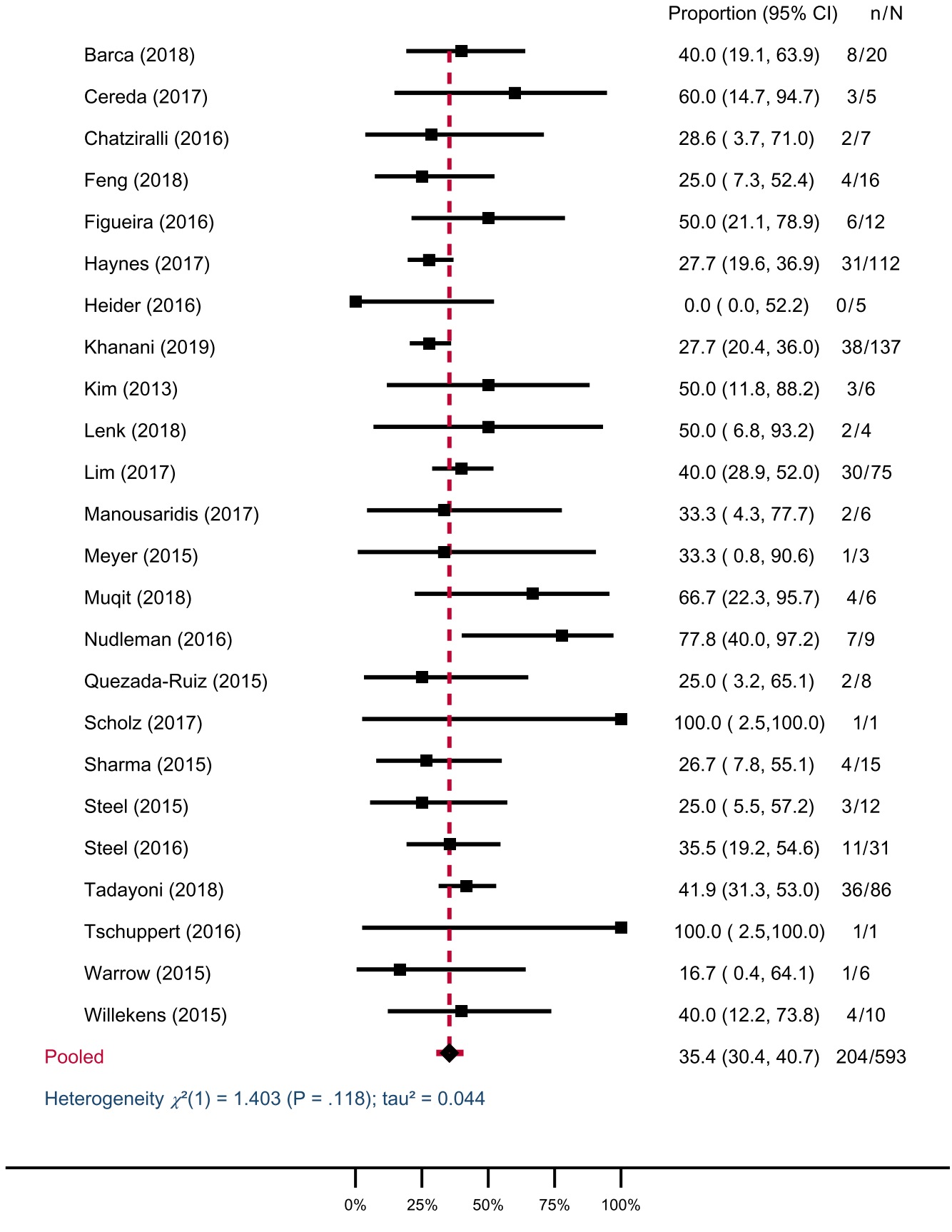

Fig. 4. Macular hole closure in real-world settings. CI = confidence interval; MH = macular hole; RWS = real-world settings.

Table 4. Effectiveness outcomes in real-world studies versus randomized trials

Outcome	RWS	RCT	OR (95% CI)	p
Nonsurgical VMAR	44.5 (39.7, 49.4)	32.5 (26.6, 39.1)	1.66 (1.18, 2.34)	0.004
Vitrectomy	19.1 (12.7, 27.6)	23.3 (15.2, 33.9)	0.85 (0.32, 2.23)	0.74
MH closure	35.4 (30.4, 40.7)	35.5 (29.0, 42.5)	1.00 (0.67, 1.50)	0.99

CI = confidence interval; MH = macular hole; OR = odds ratio; RCT = randomized controlled trial; RWS = real-world settings; VMAR = vitreomacular adhesion resolution.

Table 5. Meta-regression of prognostic covariates on effectiveness outcomes in RWS and RCTs.

Outcome	Covariate	OR (95% CI)	p	Studies	Eyes
Nonsurgical VMAR	Design	1.29 (0.93, 1.78)	0.13	17	1507
	ERM	0.20 (0.08, 0.51)	0.001		
Vitrectomy	MH	42.13 (5.02, 353.24)	0.001	27	2625

Meta-regression was carried out using a mixed effects logistic regression model with study as random effect. Study design (RCT = 0, RWS = 1), proportion of ERMs, MHs, pseudophakic status and women in the study, and age and length of follow-up were included as fixed effects in a univariate model. Covariates that were significant at the .05 level in the univariate analysis were included in a multivariate model (not shown).
CI = confidence interval; ERM = epiretinal membrane; MH = macular hole; OR = odds ratio; RCT = randomized controlled trial; RWS = real-world settings; VMAR = vitreomacular adhesion resolution.

multivariate model. Higher proportions of MH were associated with higher vitrectomy rates. Average length of follow-up was not significantly associated with improved VMAR outcomes. Study design (RWS, RCT) was not significantly associated with pVMAR, nsVMAR or vitrectomy outcomes when other covariates were taken into account.

Risk of publication bias

The funnel plots constructed for nsVMAR outcomes for VMT (Fig. 5) and MH patients (Fig. 6) show that only RCTs fell well below the 95% CI of the expected effect. Among the larger studies, one Oxurion-sponsored observational study that excluded eyes with ERM (Tadayoni et al. 2018) exceeded the expected 95% CI of the effect size for VMT patients. For the MH subgroups, the industry-sponsored RCTs remained at the low end of the efficacy estimates, while 3 RWS (Meyer et al. 2015; Nudleman et al. 2016; Tschuppert & Gerding 2016) with low numbers of MH patients reported higher than expected efficacy.

Safety outcomes in RWS studies

In general, adverse drug reactions (ADR) were inconsistently reported. To put the reported ADRs into perspective, we compared them with those from ocriplasmin-treated patients in the OASIS trial (Dugel et al. 2016). We considered the OASIS trial to be the most appropriate comparator study to the RWS because the prevalence of ERM and focal VMA was closer to that observed in the RWS, and because it was the only published RCT that used SD-OCT, and prospectively looked at inner/outer segment abnormalities, changes in photoreceptor area and thickness, (Dugel et al. 2016), full-field ERG changes (Birch et al. 2018) and microperimetry changes (Sadda et al. 2017). Table 6 shows the incidence (95% CI) of selected ADRs in the RWS studies and the corresponding incidence in the OASIS trial. The presence of photopsia and vitreous floaters, the most common adverse reactions after ocriplasmin injection (Stalmans et al. 2010; Stalmans et al. 2012; Dugel et al. 2016), was reported in only 16 and 10 studies, respectively, while the presence (or absence) of retinal detachment was reported in only 17 publications. New or worsening SRF and EZ abnormalities were reported in 22.8% (95% CI: 13.7%–35.6%) and 26.6% (95% CI: 18.0%–37.5%) of patients, respectively. In publications that reported on resolution rates of new/worsening SRF, 100 of 104 cases (96.2%) resolved. Similarly, out of 112 new/worsening EZ abnormalities, 106 (94.6%) resolved. A BCVA loss of ≥10 ETDRS letters at any time during follow-up was reported in 11 studies for an average rate of 16.1% (95% CI: 9.5%–25.9%). Lens instability was reported in 6 studies, 5 of whom reported no cases in a total of 678 eyes (Meyer et al. 2015; Quezada-Ruiz et al. 2015; Manousaridis et al., 2017; Barca et al. 2018; Khanani et al. 2019), while one study of 241 eyes (Haynes et al. 2017) reported 4 cases.

Discussion

To our knowledge, this meta-analysis of 30 real-world studies comprising 2402 patients and 2416 eyes is the largest published systematic literature review on ocriplasmin use in real-world settings to date. A similar literature review (Chatziralli et al., ,2016a, 2016b, 2016c) with a cut-off date of 30 June 2015 included 19 studies. However, that study also included eyes treated in RCTs (Stalmans et al. 2012), with only 414 of 878 eyes (47.2%) being treated in real-world settings. In addition, that meta-analysis did not take into account that the included RCTs (Stalmans et al. 2012) published nsVMAR end-points, while the RWS studies did not.

We have shown in our analysis that the nsVMAR rate was significantly higher in RWS than in RCTs and that this difference was most likely due to the proportion of ERM patients in the studies. The crude prevalence of ERM in RCTs was 263 out of 737 eyes (35.7%) while the RWS studies included 261 patients with ERM out of 1771 (14.7%).

The funnel plot comparisons of nsVMAR across RWS studies and RCTs were not suggestive of publication or industry bias. In patients with VMT, the MIVI 006 and MIVI 007 trials were well below the pooled effectiveness estimate, while the OVIID-1

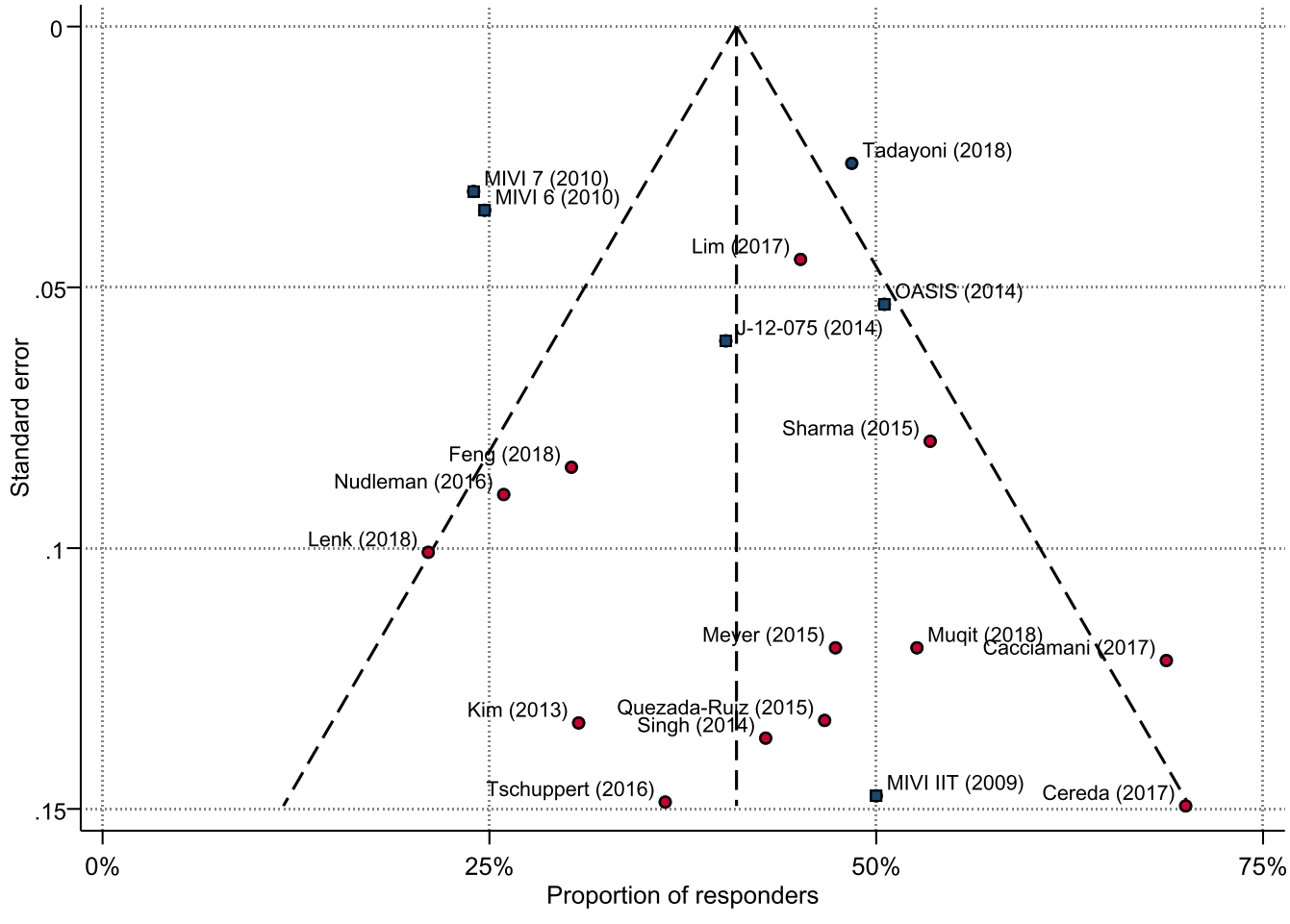

Fig. 5. Funnel plot of nsVMAR in VMT patients (RWS studies and RCTs). Squares denote RCTs, while circles denote RWS. Blue markers indicate industry sponsorship. MIVI = Microplasmin for Intravitreous Injection; MIVI-TRUST = Microplasmin for Intravitreous Injection-Traction Release without Surgical Treatment; nsVMAR = nonsurgical vitreomacular adhesion resolution; OASIS = Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole; RCT = randomized controlled trial; RWS = real-world studies; VMT = vitreomacular traction (without macular hole).

trial (Tadayoni et al. 2018) had a higher than expected effectiveness. However, given the prevalence of baseline ERM in these trials (39.7% in MIVI 006/007 and 0% in OVIID-1), these results are not unexpected. The estimates in the MH group showed similar trends, with outliers typically generated by studies with very small sample sizes.

Our ADR estimates from RWS are based on a limited number of studies and eyes. Common 'nuisance' ADRs such as photophobia and vitreous floaters were infrequently reported and were reported at a much lower frequency than what was observed in the OASIS trial. In contrast, new or worsening SRF was reported to be twice as frequent in RWS than the OASIS study, which seems to suggest a data collection/reporting bias towards ADRs that are deemed to be more clinically relevant, which can be especially important in retrospective chart reviews. In a study that prospectively monitored ADRs (including OCT findings) among 24 ocriplasmin-treated patients (Chatziralli et al., ,2016a, 2016b, 2016c), the incidence of EZ disruption (17%), SRF (17%), dyschromatopsia (4%) and MH progression (4%) was not significantly different from those observed in the OASIS trial. In that study, 6 patients (25%) developed acute vision loss, although all but 2 (8%) had recovered at the last follow-up examination.

This meta-analysis has several limitations. The vast majority of RWS were retrospective in nature and therefore had no preplanned data collection or follow-up schedule. The reporting of VMAR outcomes, as well as that of established prognostic risk factors such as age, sex and ERM/MH/phakic status in RWS, was often incomplete. These factors limited our meta-regression to the overall population since risk factor prevalence was rarely available for MH/VMT subgroups. Also, adding multiple covariates into the model quickly resulted in decreasing numbers of studies and eyes in the analysis.

A challenge in any meta-analysis of retrospectively collected data is the variability of the time-point at which outcomes are measured. We tried to mitigate this problem by excluding studies with a mean follow-up duration of less than 4 weeks, since it has been shown that that in a mixed population of VMT and MH patients, nsVMAR quickly reaches a plateau at 28 days that remains relatively stable thereafter (Stalmans et al. 2012; Dugel et al. 2016). It was therefore not entirely unexpected that no association was observed between length of follow-up

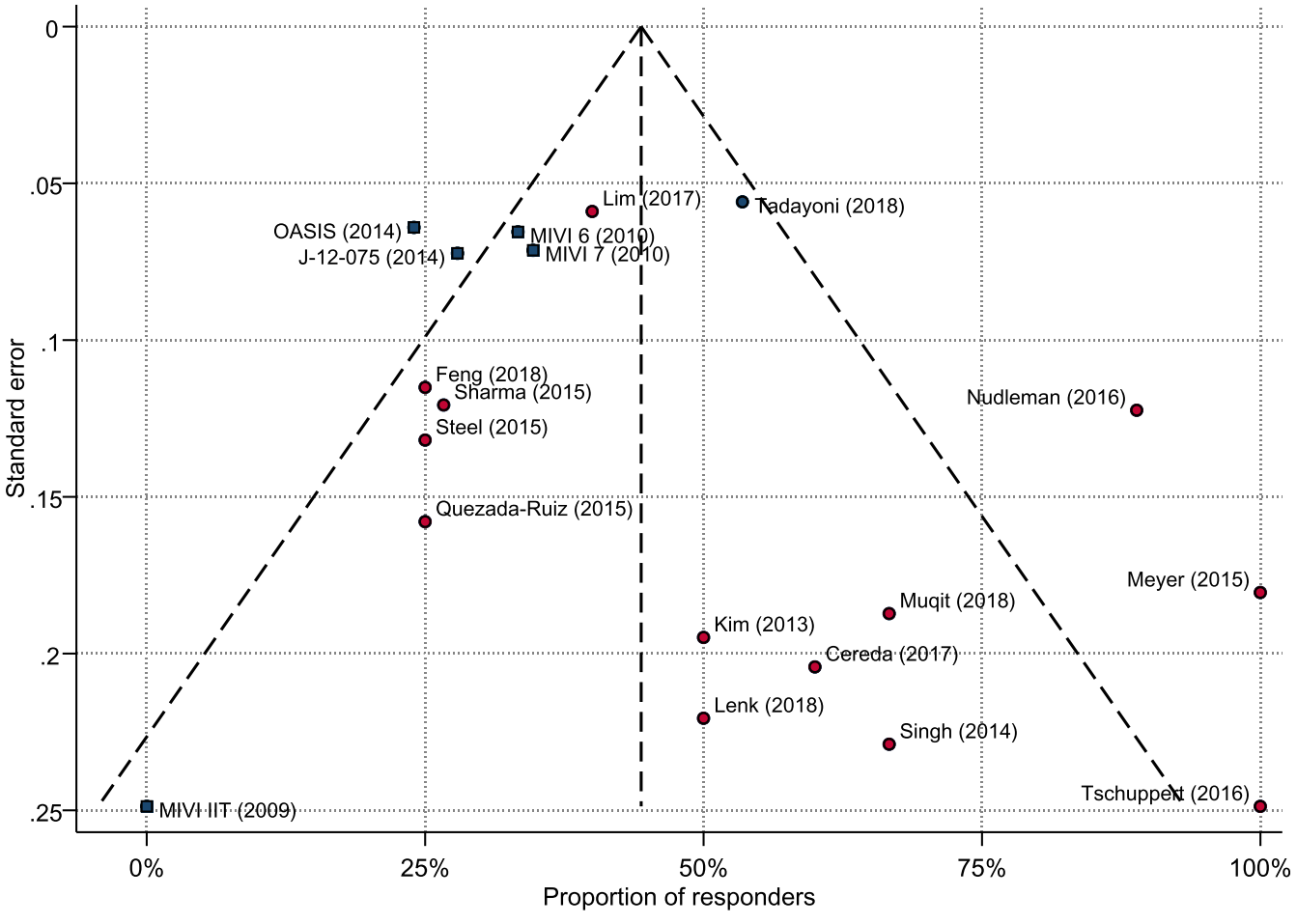

Fig. 6. Funnel plot of nsVMAR in MH patients (RWS studies and RCTs). Squares denote RCTs, while circles denote RWS. Blue markers indicate industry sponsorship. MH = macular hole; MIVI = Microplasmin for Intravitreous Injection; MIVI-TRUST = Microplasmin for Intravitreous Injection-Traction Release without Surgical Treatment; OASIS = Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole; RCT = randomized controlled trial; RWS = real-world settings; nsVMAR = nonsurgical vitreomacular adhesion resolution.

Table 6. Safety outcomes as reported in real-world settings, compared with the OASIS trial

Event	Studies reporting event	Events reported	Patient total	RWS studies % (95% CI)	OASIS % (95% CI)
Photophobia	7	54	1368	3.9 (3.0, 5.1)	13.0 (8.0, 19.6)
Photopsia	16	362	1901	22.3 (16.3, 29.6)	29.5 (22.2, 37.6)
Floaters	10	120	827	22.4 (13.6, 34.6)	37.7 (29.8, 46.1)
Dyschromatopsia	12	102	1705	9.5 (4.4, 19.4)	11.0 (6.4, 17.2)
Retinal detachment	17	42	1812	2.2 (1.4, 3.3)	1.3 (0.2, 4.9)
Retinal tear	9	21	1097	1.2 (0.3, 5.4)	1.3 (0.2, 4.9)
Subretinal fluid[a]	16	152	1060	22.8 (13.7, 35.6)	11.6 (6.9, 18.0)
EZ abnormal[a]	15	156	732	26.6 (18.0, 37.5)	21.4 (14.9, 29.2)
ERG abnormal[a]	3	9	250	3.6 (1.9, 6.8)	40.0 (24.9, 56.7)
MH progression[a]	5	71	795	10.3 (4.3, 22.4)	15.8 (10.3, 22.7)
BCVA ≥ 2-line loss[b]	12	246	1277	16.1 (9.5, 25.9)	12.5 (7.6, 19.0)

BCVA = best-corrected visual acuity (Early Treatment Diabetic Retinopathy Study letters); CI = confidence interval; ERG = electroretinogram; EZ = ellipsoid zone; MH = macular hole; OASIS = Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole; RWS = real-world settings.

[a] New or worsening.

[b] Numbers for OASIS represent patients who had ≥10-letter BCVA loss at any point prior to vitrectomy, regardless of subsequent improvement.

and nsVMAR incidence. Given the average length of follow-up in the RWS (20.9 weeks), we chose the 6-month time-point for the analysis of the RCTs. Had we chosen the 3-month time-point instead, more than 40% of vitrectomies would not have been taken into account, which would have biased the results towards a higher

nsVMAR incidence, as well as lower vitrectomy numbers.

Similarly, reporting of VMAR outcomes was inconsistent, with most authors not mentioning the incidence of vitrectomy after successful pVMAR. Eight out of 30 RWS (27%) did not mention vitrectomy at all. The lack of attention to this common outcome is concerning and should be addressed in future studies. Lastly, we were unable to evaluate the effectiveness of ocriplasmin in improving BCVA in RWS studies, since the reported data did not allow for such an analysis.

The main strength of this meta-analysis resides in the size of the dataset and the diverse origin of patients. Despite the fact that the two largest RWS (comprising 1005 of the total of 2416 eyes – 41.6%) (Tadayoni et al. 2018; Khanani et al. 2019) were sponsored by the manufacturer of ocriplasmin, the pooled overall nsVMAR rate for the independent RWS studies was not different from that of the industry-sponsored RWS studies in a mixed effects model with study as random effect and baseline ERM as fixed effect: OR 1.19 (95% CI: 0.82–1.73; $p = 0.35$). It is therefore unlikely that industry sponsorship resulted in a favourable effectiveness bias for ocriplasmin.

Our study supports the hypothesis that improved patient selection (i.e. avoiding treatment of eyes with ERM) is associated with higher rates of nsVMAR in RWS compared with RCTs. The incidence of vitrectomy and MH closure in RWS is consistent with that seen in RCTs. This review shows also that there is a need for improved reporting standards for VMT disease and relevant treatment outcomes.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 RWS quality assessment grid[a].
Fig. S2 Risk of bias in RCTs.
Table S1 EMBASE search terms for real-world ocriplasmin studies (June 5, 2019).
Table S2 EMBASE search te 1 rms for ocriplasmin randomized controlled trials (June 5, 2019).