Supplementary Material

Efficacy and Safety of Ocriplasmin Use for Vitreomacular Adhesion and its Predictive Factors: a systematic review and meta-analysis

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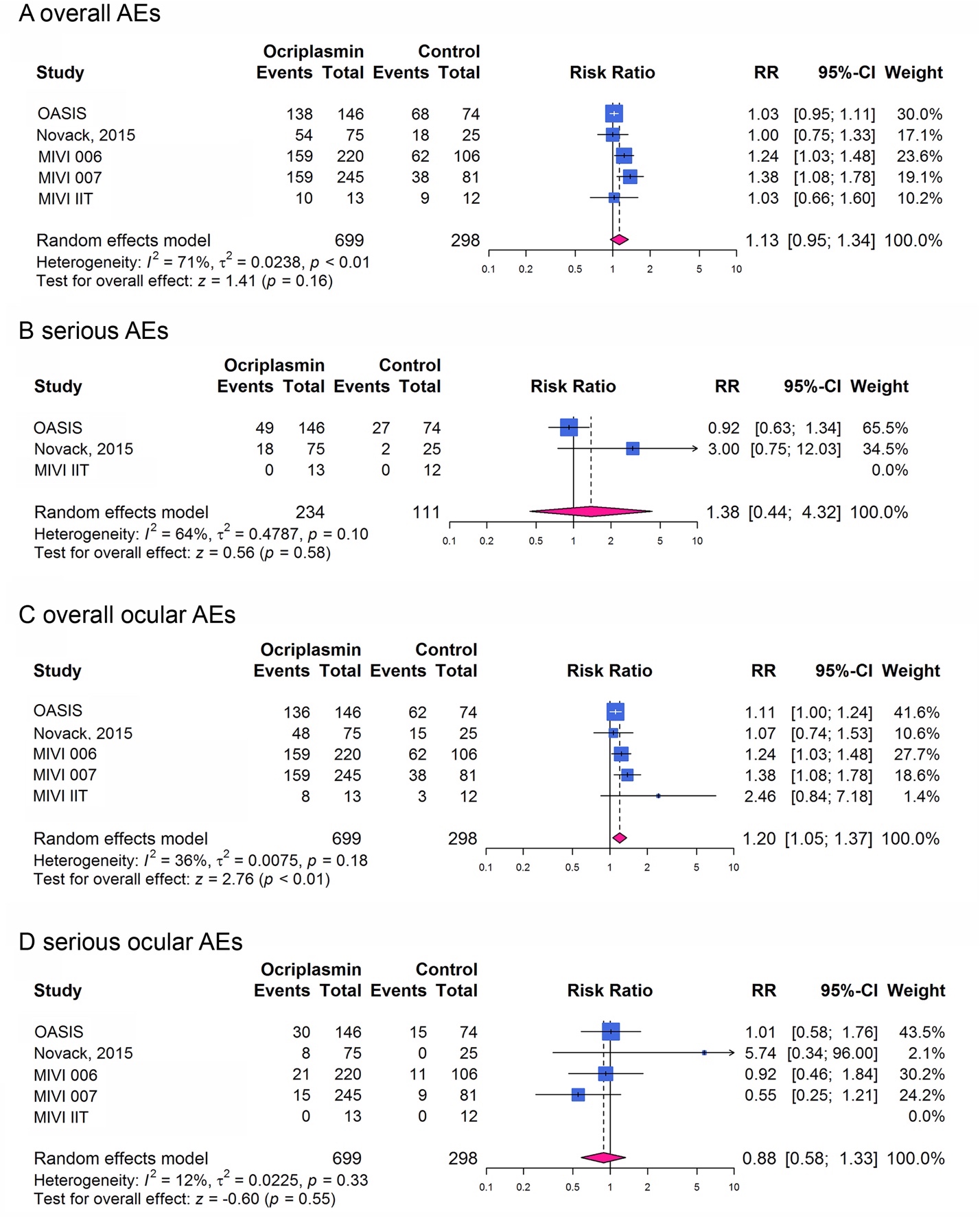
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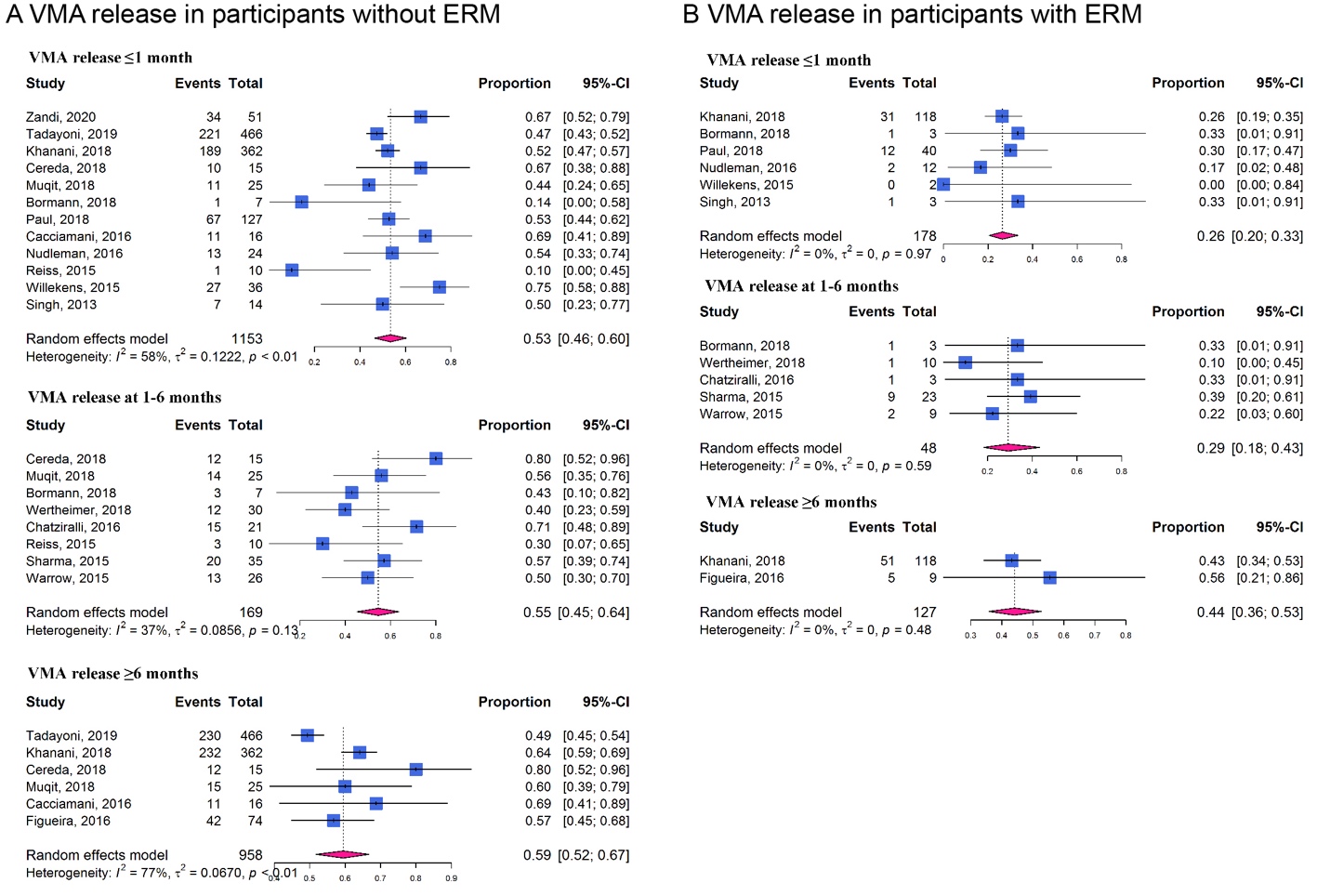
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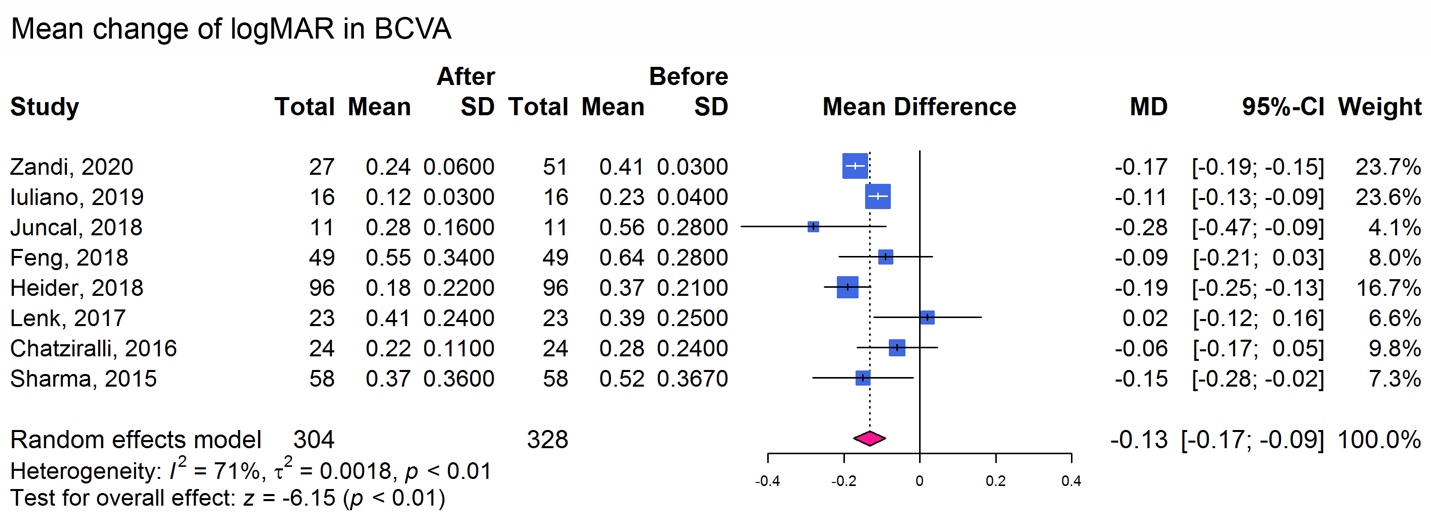
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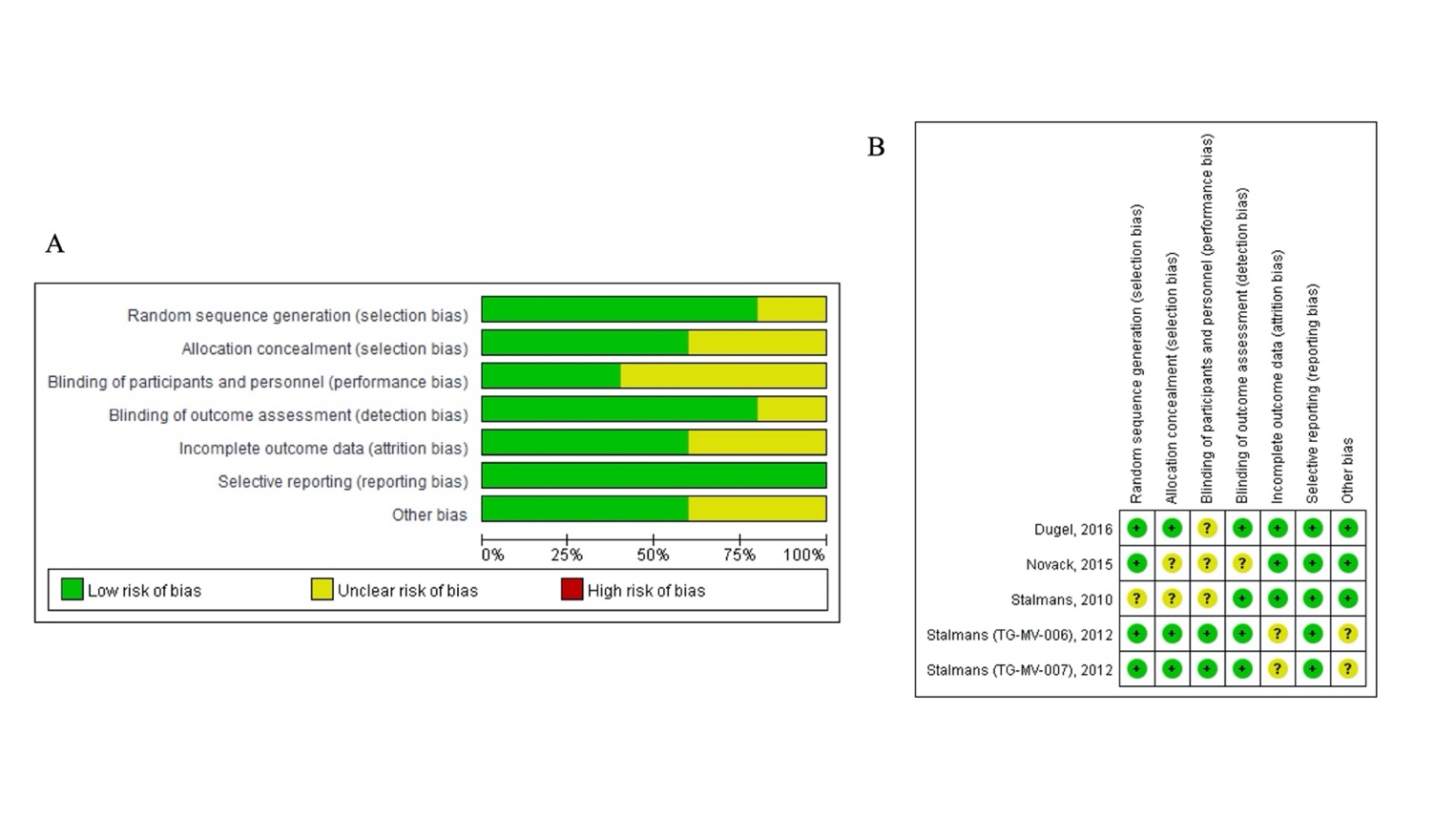
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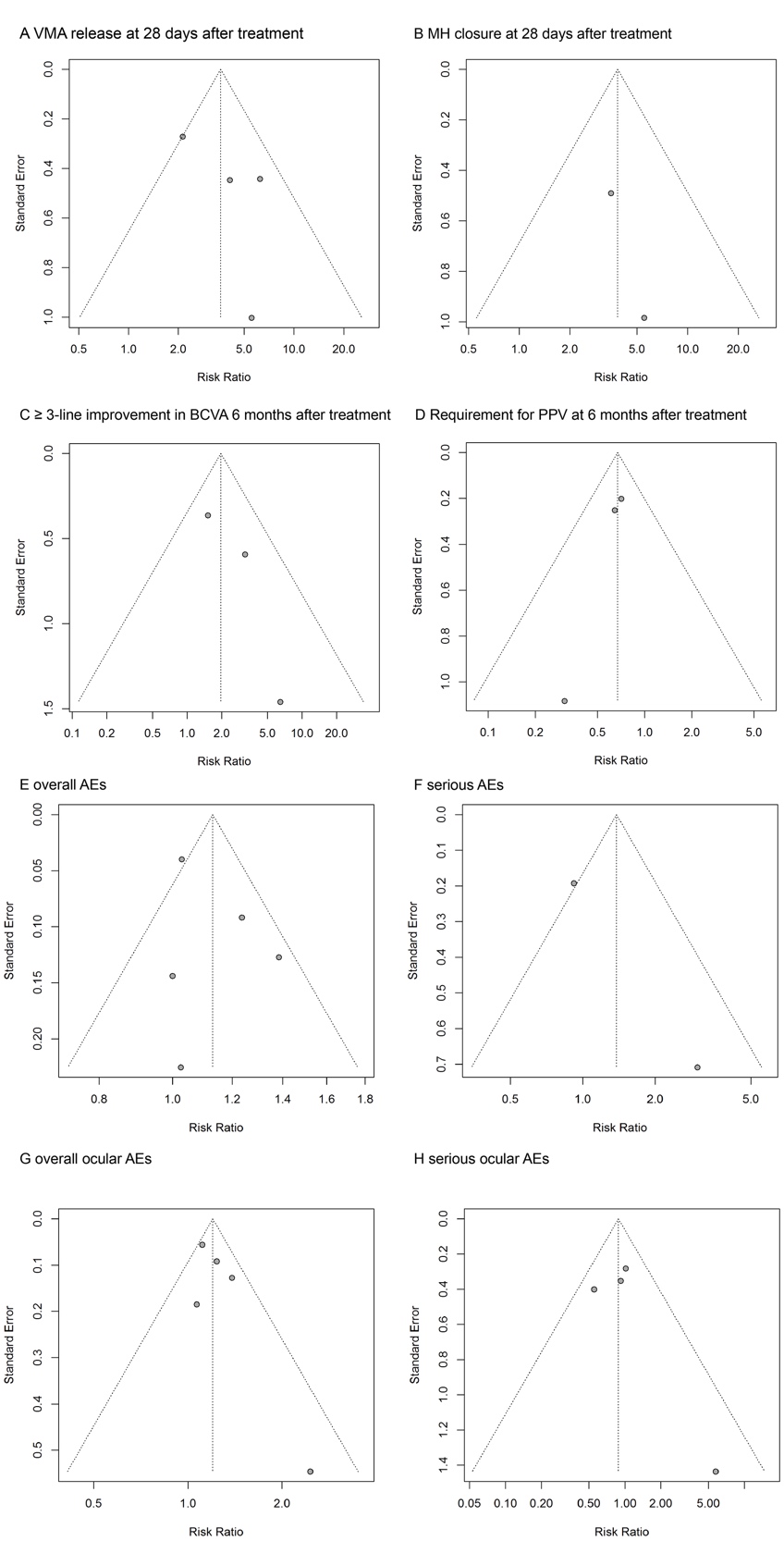
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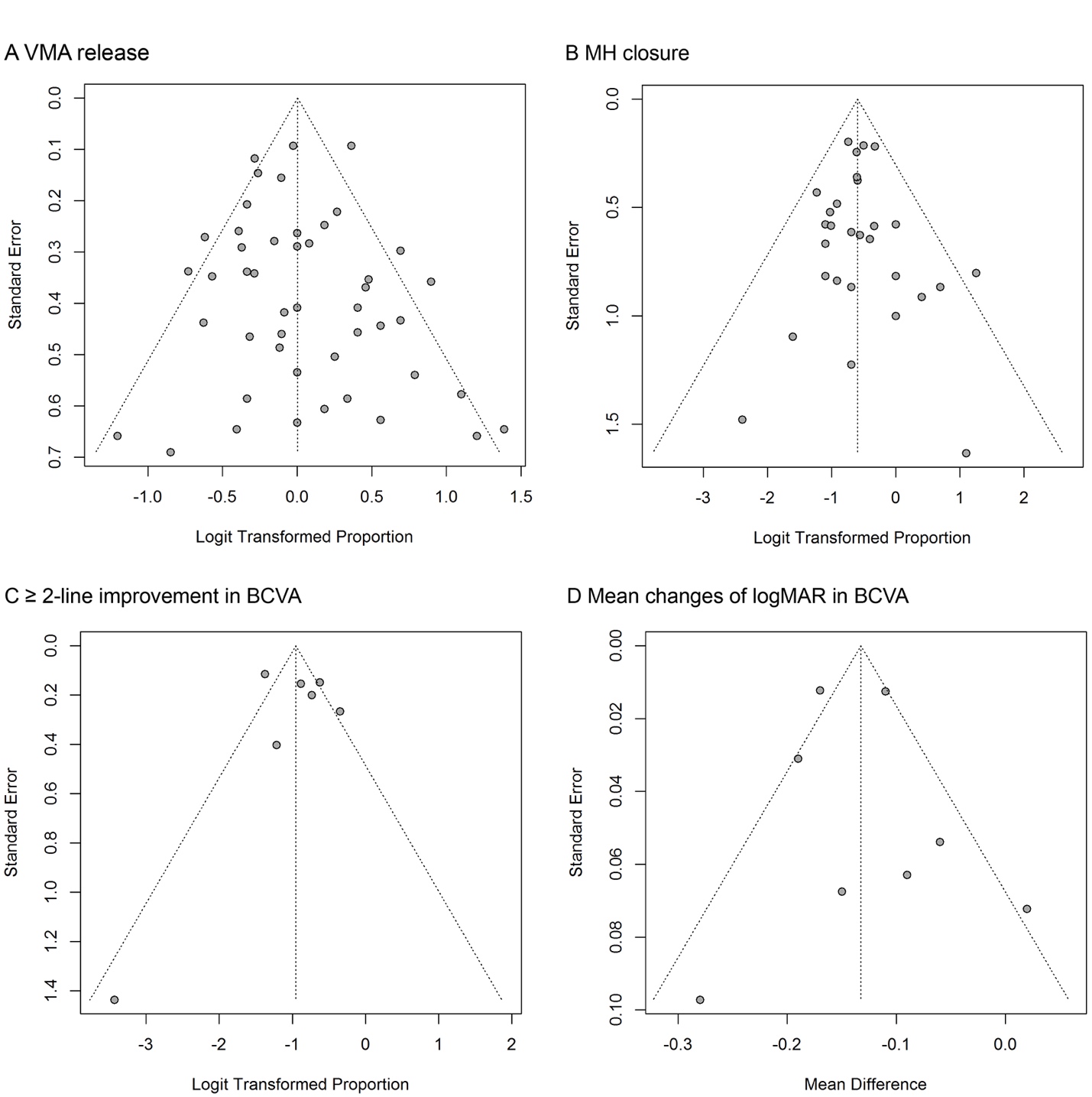
**Supplementary Figure 2.** Forest plots of proportion of vitreomacular adhesion (VMA) release in participants with or without epiretinal membrane (ERM) at different time points after receiving ocriplasmin therapy. (**A**) in participants without ERM; (**B**) in participants with ERM

**Supplementary Figure 3.** Forest plots of mean change of logMAR in best-corrected visual acuity after ocriplasmin therapy in included cohort studies



**Supplementary Figure 4. Quality assessment of included randomized control trails.** A, risk of bias item presented as percentages across included studies, B, list of each risk of bias item for each included study

**Supplementary Figure 5. Funnel plots for publication bias assessment of included randomized control trails.** A, for VMA release at 28 days after treatment; B, for macular hole (MH) closure at 28 days after treatment; C, for at least 3-line improvement in best-corrected visual acuity (BCVA) at 6 months after treatment; D, for incidence of pars plana vitrectomy (PPV) at 6 months after treatment; E, for incidence of all AEs; F, for incidence of any serious AEs; G, for incidence of all ocular AEs; H, for incidence of any serious ocular AEs.

**Supplementary Figure 6. Funnel plots for publication bias assessment of included cohort studies.** A, for proportion of VMA release; B, for proportion of MH closure; C, for proportion of ≥ 2-line improvement in BCVA; D, for mean changes of logMAR in BCVA.

**Supplementary Table 1. Characteristics of the 55 studies included in the meta-analysis**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No | First author | Year | Country | Design | Sample size | Male/ Female | Age, year | Intervention | Follow-up duration |
| 1 | Dugel (1, 2) (OASIS) | 2016 | United States | RCT | 220 | 71/149 | 69.1 ± 10.34 | 125 μg ocriplasmin intravitreal injection or sham injection | 1 to 24 months |
| 2 | Novack (3) | 2015 | United States and Europe | RCT | 100 | 45/55 | 74.6 ± 7.86 | 125 μg ocriplasmin intravitreal injection or sham injection | 7 days to 12 months |
| 3 | Stalmans (4-6)  (MIVI 006) | 2012 | United States | RCT | 326 | 119/207 | 71.4 (range 18–96) | 125 μg ocriplasmin intravitreal injection or sham injection | 180 days |
| 4 | Stalmans (4-6)  (MIVI 007) | 2012 | United States and Europe | RCT | 326 | 104/222 | 72.0 (range 23–97) | 125 μg ocriplasmin intravitreal injection or sham injection | 180 days |
| 5 | Stalmans (7) (MIVI-IIT) | 2010 | Belgium | RCT | 25 | 11/14 | 72.1 (range 53–84) | Only include patients received 125 μg ocriplasmin intravitreal injection or sham injection | 3, 7, 14, 28, 90 and 180 days |
| 6 | Steel (8) (INJECT) | 2020 | Europe | Prospective cohort | 428 | 143/285 | 74.0 (quartile 67.0–79.0) | 125 μg ocriplasmin intravitreal injection | 14 and 28 days, 6, and 12 months |
| 7 | Zandi (9) | 2020 | United States | Retrospective case series | 51 | 19/32 | 76 ± 8 | 125 μg ocriplasmin intravitreal injection | 24 ± 14 months |
| 8 | Cacciamani (10) | 2020 | Italy | Prospective cohort | 23 | 5/18 | 69.5 ± 8.2 | 125 μg ocriplasmin intravitreal injection | 1 and 4 weeks |
| 9 | Tadayoni (11)(OVIID-1) | 2019 | Europe and Canada | Prospective cohort | 466 | 122/344 | 71.7 ± 8.3 | 125 μg ocriplasmin intravitreal injection | 28 to 180 days |
| 10 | Iuliano (12) | 2019 | Italy | Prospective cohort | 16 | 7/9 | 59.2 ± 3.4 | 125 μg ocriplasmin intravitreal injection | 1 month |
| 11 | Grinton a (13) | 2019 | England | Retrospective case series | 81 | NR | NR | ocriplasmin intravitreal injection | 4 weeks |
| 12 | Khanani (14) (ORBIT) | 2018 | United States | Prospective cohort | 480 | 171/309 | 71.3 ± 8.21 | 125 μg ocriplasmin intravitreal injection | 1 to 12 months |
| 13 | Cereda (15) | 2018 | Italy | Retrospective case series | 15 | 5/15 | 70 (range 45–84) | 125 μg ocriplasmin intravitreal injection | 1 week, 1, 3 and 6 months |
| 14 | Muqit (16)  (IPD study) | 2018 | United Kingdom | Retrospective case series | 25 | 8/17 | 71 | 125 μg ocriplasmin intravitreal injection | 4, 12, and 24 weeks |
| 15 | Bormann (17)  (IPD study) | 2018 | Germany | Retrospective case series | 10 | 3/7 | 75.1 (range 63–84) | 125 μg ocriplasmin intravitreal injection | 8 weeks |
| 16 | Feng (18) | 2018 | United States | Retrospective case series | 49 | 16/33 | 71 ± 10 | 125 μg ocriplasmin intravitreal injection | 10.3 ± 2.0 months |
| 17 | Paul (19) | 2018 | Germany | Retrospective case series | 167 | 49/118 | 72.7 ± 8.9 | ocriplasmin intravitreal injection | 28 ± 5 days |
| 18 | Wertheimer (20) | 2018 | Germany | Retrospective case series | 40 | 14/26 | 73 ± 9.5 | 125 μg ocriplasmin intravitreal injection | 1, 4, 12, and 24 weeks |
| 19 | Heider (21) | 2018 | Germany | Retrospective case series | 96 | 41/55 | 70.8 | ocriplasmin intravitreal injection | 7.13 ± 6.40 months |
| 20 | Wan a (22) | 2018 | Australia | Retrospective case series | 13 | NR | NR | ocriplasmin intravitreal injection | 7, 28, 90 and 180 days |
| 21 | Juncal (23) | 2018 | Canada | Retrospective case series | 11 | NR | 68.3 ± 8.74 | 125 μg ocriplasmin intravitreal injection | 13.6 (range 6-36) months |
| 22 | Manousaridis (24) | 2017 | Austria | Retrospective case series | 20 | NR | 68.5 (range 21–88) | 125 μg ocriplasmin intravitreal injection | 28 days |
| 23 | Lim (25) | 2017 | United States and United Kingdom | Retrospective case series | 208 | NR | NR | ocriplasmin intravitreal injection | at least 3 weeks |
| 24 | Scholz (26) | 2017 | Switzerland | Retrospective case series | 14 | 2/12 | 73 ± 10 | ocriplasmin intravitreal injection | 2 weeks and 4 months |
| 25 | Gkizis a (27) | 2017 | NR | Retrospective case series | 10 | 2/8 | NR | ocriplasmin intravitreal injection | 1, 7 and 28 days |
| 26 | Tacea a (28) | 2017 | United Kingdom | Retrospective case series | 33 | 10/23 | NR | ocriplasmin intravitreal injection | 1, 3 and 12 months |
| 27 | Zakri a (29) | 2017 | United Kingdom | Retrospective case series | 60 | 30/30 | 75 | ocriplasmin intravitreal injection | NR |
| 28 | Robson a (30) | 2017 | United Kingdom | Retrospective case series | 48 | 25/23 | 76.8 | ocriplasmin intravitreal injection | mean 39.8 days |
| 29 | Patel a (31) | 2017 | United States | Retrospective case series | 66 | NR | NR | 125 μg ocriplasmin intravitreal injection | 1 week, 1, 3, 6 and 12 months |
| 30 | Lenk (32) | 2017 | Germany | Retrospective case series | 21 | NR | NR | ocriplasmin intravitreal injection | NR |
| 31 | Itoh (33) | 2017 | United Kingdom | Retrospective case series | 19 | NR | NR | 125 μg ocriplasmin intravitreal injection | 1 week, 1 and 3 months |
| 32 | Cacciamani (34) | 2016 | Italy | Retrospective case series | 15 | 6/9 | 55.1 ± 4.6 | 125 μg ocriplasmin intravitreal injection | 6 months |
| 33 | Michalska-Malecka (35) | 2016 | Poland | Retrospective case series | 16 | NR | 75.6 ± 6.04 | 125 μg ocriplasmin intravitreal injection | 1 day, 1 week and 1 month |
| 34 | Tschuppert (36) | 2016 | Switzerland | Retrospective case series | 12 | NR | NR | 125 μg ocriplasmin intravitreal injection | 3, 10, 29 days to 4 months |
| 35 | Nudleman (37) | 2016 | United States | Retrospective case series | 35 | 10/25 | 74.1 (range 48.7–88.9) | ocriplasmin intravitreal injection | 1, 6 and 12 months |
| 36 | Steel (38) | 2016 | United Kingdom | Prospective cohort | 31 | 9/22 | 71 ± 6 | 125 μg ocriplasmin intravitreal injection | 4–6 weeks |
| 37 | Figueira (39) | 2016 | Portugal | Retrospective case series | 78 | 24/54 | 70.9 ± 8.7 | 125 μg ocriplasmin intravitreal injection | at least 1 month |
| 38 | Chatziralli (40) | 2016 | Greece | Prospective cohort | 24 | 8/16 | 71.4 ± 8.7 | 125 μg ocriplasmin intravitreal injection | 1, 7, 28 to 127 days |
| 39 | Sharma a (41) | 2016 | United States | Retrospective case series | 34 | NR | NR | ocriplasmin intravitreal injection | mean 13.6 months |
| 40 | Preziosa a (42) | 2016 | Italy | Retrospective case series | 13 | NR | NR | ocriplasmin intravitreal injection | 1 week, 1, 3 and 6 months |
| 41 | Atkins a (43) | 2016 | United Kingdom | Retrospective case series | 10 | NR | NR | 125 μg ocriplasmin intravitreal injection | 1 month |
| 42 | Steel (44)  (IPD study) | 2015 | United Kingdom | Prospective cohort | 12 | 3/9 | 72.6 ± 3.8 | 125 μg ocriplasmin intravitreal injection | 1 and 4 weeks |
| 43 | Quezada-Ruiz (45) | 2015 | United States | Retrospective case series | 23 | 6/17 | 74 (range 53–93) | ocriplasmin intravitreal injection | 174 (range 20–291) days |
| 44 | Reiss (46) | 2015 | United States | Retrospective case series | 10 | 4/6 | 73 ± 11.1 | ocriplasmin intravitreal injection | at least 28 days |
| 45 | Willekens (47)  (IPD study) | 2015 | Portugal | Retrospective case series | 37 | 8/29 | 73.7 ± 4.0 | ocriplasmin intravitreal injection | at least 28 days |
| 46 | Sharma (48) | 2015 | United States | Retrospective case series | 58 | 20/38 | 72 (range 59–94) | 125 μg ocriplasmin intravitreal injection | mean 8.7 months |
| 47 | Meyer a (49) | 2015 | United States | Retrospective case series | 22 | NR | NR | ocriplasmin intravitreal injection | at least 1 week |
| 48 | Warrow (50)  (IPD study) | 2015 | United States | Retrospective case series | 35 | 12/23 | 69.4 | 125 μg ocriplasmin intravitreal injection | 96.3 (range 7–211) days |
| 49 | Dyer a (51) | 2015 | United States | Retrospective case series | 34 | 19/15 | NR | ocriplasmin intravitreal injection | 1, 3, 6 and 12 months |
| 50 | Zhao a (52) | 2015 | United States | Retrospective case series | 19 | NR | NR | 125 μg ocriplasmin intravitreal injection | 7 days to 1 year |
| 51 | Coskey a (53) | 2014 | United States | Retrospective case series | 52 | NR | NR | ocriplasmin intravitreal injection | up to 9 months |
| 52 | Steinle a (54) | 2014 | United States | Retrospective case series | 24 | NR | 73 (range 53–93) | ocriplasmin intravitreal injection | 168 (range 20-291) days |
| 53 | Roth a (55) | 2014 | United States | Retrospective case series | 62 | NR | NR | 125 μg ocriplasmin intravitreal injection | 1 week and 1 month |
| 54 | Singh (56) | 2014 | United States | Retrospective case series | 17 | 6/11 | 68.8 ± 9.03 | 125 μg ocriplasmin intravitreal injection | 28 days |
| 55 | Kim a (57) | 2013 | United States | Retrospective case series | 19 | NR | NR | ocriplasmin intravitreal injection | NR |

Data were presented by percent or median (range)

Abbreviations: NR, not reported

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**Supplementary Table 2**. Characteristics of participants achieving or not achieving vitreomacular adhesion release after ocriplasmin treatment

|  |  |  |
| --- | --- | --- |
| Events | Estimation of merged value | |
| VMA release | VMA persistence |
| Female (%) | 149/203 | 120/195 |
| Absence of ERM (%) | 153/171 | 123/170 |
| Age (y) | 69.29 (67.58, 71.00) | 74.90 (73.82, 75.97) |
| VMA diameter | 384.10 (314.88, 453.32) | 572.17 (460.00, 684.33) |
| CRT | 365.63 (338.72, 392.55) | 369.22 (342.03, 396.41) |

Abbreviations: VMA, vitreomacular adhesion; ERM, epiretinal membrane; CRT, central retinal thickness; data presents as mean (95% confidence intervals) for age, VMA diameter and CRT.

**Supplementary Table 3**. Characteristics of participants achieving or not achieving macular hole closure after ocriplasmin treatment

|  |  |  |
| --- | --- | --- |
| Events | Estimation of merged value | |
| MH closure | MH persistence |
| Female (%) | 19/24 | 30/39 |
| Age (y) | 67.42 (63.45, 71.38) | 72.55 (69.73, 75.36) |
| VMA diameter | 290.84 (266.09, 315.60) | 240.92 (122.04, 359.81) |
| MH base diameter | 307.56 (250.73, 364.39) | 649.91 (485.42, 814.41) |
| MH minimum linear diameter | 235.87 (188.61, 283.14) | 271.11 (231.10, 311.13) |

Abbreviations: MH, macular hole; VMA, vitreomacular adhesion; data presents as mean (95% confidence intervals) for VMA diameter, MH base diameter and MH minimum linear diameter.

**Supplementary Table 4**. **Characteristics of the individual participant data analysis studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No | Study | Sample size | Male/ Female | Age, year | VMA release incidence | Proportion of MH | Proportion of ERM | VMA diameter  (mean ± SD) | Follow-up duration |
| 1 | Muqit, 2018 (16) | 25 | 8/17 | 71 | 15/25 | 6/25 | 0/25 | 524.7 ± 202.5 | 4, 12, and 24 weeks |
| 2 | Bormann, 2018 (17) | 10 | 3/7 | 75.1 (range 63–84) | 4/10 | 5/10 | 3/10 | NR | 8 weeks |
| 3 | Steel, 2015 (44) | 12 | 3/9 | 72.6 ± 3.8 | 7/12 | 12/12 | NR | 210.8 | 1 and 4 weeks |
| 4 | Willekens, 2015 (47) | 37 | 8/29 | 73.7 ± 4.0 | 27/37 | 10/37 | 2/37 | 387.2 ± 424.7 | at least 28 days |
| 5 | Warrow, 2015 (50) | 35 | 12/23 | 69.4 | 15/35 | 6/35 | 9/35 | 571.1 ± 439.7 | 96.3 (range 7–211) days |

Abbreviations: VMA, vitreomacular adhesion; MH, macular hole; ERM, epiretinal membrane; SD, standard deviation; NR, not reported

**Supplementary Table 5. Receiver operating characteristic curve analysis for predicting factors affecting vitreomacular adhesion release**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variables | Sample size | AUROC (95% CI) | Sensitivity | Specificity | Cut-off value |
| VMA diameter | 92 | 0.71 (0.61-0.80) | 81.13 (68.0-90.6) | 56.41 (39.6-72.2) | 506 |
| Age | 120 | 0.62 (0.53-0.71) | 66.18 (53.7-77.2) | 57.69 (43.2-71.3) | 73 |
| ERM formation | 83 | 0.62 (0.50-0.72) | 93.48 (82.1-98.6) | 29.73 (15.9-47.0) | No |
| Female | 120 | 0.59 (0.50-0.68) | 77.94 (66.2-87.1) | 40.38 (27.0-54.9) | No |
| MH | 120 | 0.57 (0.47-0.66) | 38.24 (26.7-50.8) | 75.00 (61.1-86.0) | No |
| Combined | 73 | 0.84 (0.74-0.92) | 73.81 (58.0-86.1) | 83.87 (66.3-94.5) | 0.68 |

*Prelease*=1/[1+exp(0.004\*VMA diameter-1.896\*female(1=Yes, 0=No)+2.174\*ERM(1=Yes, 0=No) )]

Abbreviations: ROC, receiver operating characteristic curves; VMA, vitreomacular adhesion; AUROC, areas under ROCs; ERM, epiretinal membrane; MH, macular hole

**Supplementary Table 6. Some examples in the predict model for vitreomacular adhesion release**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Subject 6 |
| Age | 65 | 65 | 65 | 65 | 75 | 75 |
| Sex | Female | Male | Female | Male | Female | Male |
| VMA diameter (μm) | 100 | 100 | 300 | 300 | 600 | 600 |
| ERM | No | No | No | No | No | No |
| *Prelease* | 0.82 | 0.40 | 0.68 | 0.23 | 0.38 | 0.08 |

Abbreviations: VMA, vitreomacular adhesion; ERM, epiretinal membrane

**Supplementary Table 7. Analysis of different etiologies affecting vitreomacular adhesion release**

|  |  |  |  |
| --- | --- | --- | --- |
| Subgroup Analysis | No. of Studies | Rate of VMA Release | *I2* (%) |
| % of AMD |  |  |  |
| > 20% | 4 | 0.48 (0.39-0.57) | 0.0% |
| < 20% | 5 | 0.47 (0.36-0.57) | 73.2% |
| % of DR |  |  |  |
| > 10% | 6 | 0.44 (0.39-0.49) | 0.0% |
| < 10% | 5 | 0.44 (0.39-0.49) | 0.0% |
| % of RVO |  |  |  |
| > 4% | 2 | 0.43 (0.32-0.54) | 0.0% |
| < 4% | 1 | 0.43 (0.37-0.49) | - |

Abbreviations: VMA, vitreomacular adhesion; AMD, age-related macular degeneration; DR, diabetic retinopathy; RVO, retinal vein occlusion

**Supplementary Table 8. Quality assessment of included cohort studies**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 | Q14 | Q15 | Q16 | Q17 | Q18 | Q19 | Q20 |
| Steel, 2020 | Y | Y | Y | U | N | N | U | N | N | Y | U | Y | Y | Y | Y | N | N | Y | Y | N |
| Zandi, 2020 | Y | N | U | U | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Cacciamani, 2020 | Y | Y | Y | U | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Tadayoni, 2019 | Y | Y | Y | U | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Iuliano, 2019 | Y | Y | N | Y | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | N | Y | Y |
| Grinton, 2019 | Y | N | Y | U | Y | N | U | N | N | Y | U | Y | N | U | Y | Y | Y | N | Y | N |
| Khanani, 2018 | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Cereda, 2018 | Y | N | N | U | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | N | Y | Y | P |
| Muqit, 2018 | Y | N | N | Y | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | N | Y | Y | Y |
| Bormann, 2018 | Y | N | N | U | Y | N | Y | Y | N | Y | U | Y | Y | Y | Y | Y | N | N | Y | P |
| Feng, 2018 | Y | N | N | Y | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Paul, 2018 | Y | N | Y | Y | Y | Y | Y | N | N | N | U | Y | Y | Y | U | N | Y | N | Y | P |
| Wertheimer, 2018 | Y | N | N | Y | Y | Y | Y | Y | N | Y | U | Y | Y | Y | U | Y | Y | Y | Y | P |
| Heider, 2018 | Y | U | U | U | N | N | Y | N | N | N | U | Y | N | U | Y | Y | Y | N | Y | N |
| Wan, 2018 | Y | U | U | U | N | N | Y | N | N | Y | U | Y | Y | U | Y | N | Y | N | Y | N |
| Juncal, 2018 | Y | N | Y | U | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | N |
| Manousaridis, 2017 | Y | N | N | U | Y | N | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Lim, 2017 | Y | N | U | U | Y | N | Y | N | N | N | U | Y | Y | Y | Y | N | Y | Y | Y | Y |
| Itoh, 2017 | Y | N | N | Y | P | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Scholz, 2017 | Y | N | Y | U | Y | N | Y | N | N | Y | U | Y | Y | Y | Y | Y | Y | N | Y | P |
| Gkizis, 2017 | Y | U | N | U | Y | N | Y | N | N | P | U | Y | U | U | Y | Y | N | Y | Y | N |
| Tacea, 2017 | Y | N | U | U | Y | N | Y | N | N | P | U | Y | U | U | Y | Y | N | Y | Y | N |
| Zakri, 2017 | Y | N | Y | U | Y | N | Y | N | N | P | U | Y | U | U | U | N | N | N | Y | N |
| Robson, 2017 | Y | N | U | U | Y | N | Y | N | N | Y | U | Y | Y | U | Y | Y | Y | Y | Y | N |
| Patel, 2017 | Y | N | U | U | N | N | Y | Y | N | Y | U | Y | Y | U | Y | Y | N | N | Y | N |
| Lenk, 2017 | Y | N | U | U | N | N | Y | N | N | Y | U | Y | Y | Y | U | Y | Y | N | Y | N |
| Cacciamani, 2016 | Y | U | Y | Y | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Michalska-Malecka, 2016 | Y | N | Y | U | Y | N | Y | Y | N | Y | U | Y | Y | U | Y | Y | Y | Y | Y | N |
| Tschuppert, 2016 | Y | N | U | Y | N | N | Y | Y | N | N | U | Y | N | U | Y | Y | Y | N | Y | P |
| Nudleman, 2016 | Y | N | N | U | Y | Y | Y | N | N | Y | U | Y | Y | U | Y | Y | Y | N | Y | Y |
| Steel, 2016 | Y | Y | Y | U | Y | P | Y | N | N | N | U | Y | Y | Y | Y | Y | Y | N | Y | P |
| Figueira, 2016 | Y | N | Y | U | Y | Y | Y | Y | N | N | U | Y | Y | Y | Y | Y | Y | N | Y | Y |
| Chatziralli, 2016 | Y | Y | Y | U | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | P |
| Sharma, 2016 | Y | N | N | U | N | N | Y | N | N | P | U | Y | Y | U | Y | Y | N | N | Y | N |
| Preziosa, 2016 | Y | N | U | U | N | N | Y | N | N | Y | U | Y | Y | Y | Y | Y | N | N | Y | N |
| Atkins, 2016 | Y | N | U | U | N | N | Y | Y | N | P | U | Y | N | U | Y | N | N | Y | Y | N |
| Steel, 2015 | Y | Y | U | Y | Y | P | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | N | Y | Y |
| Quezada-Ruiz, 2015 | Y | N | N | Y | Y | Y | Y | N | N | P | U | Y | Y | Y | Y | Y | Y | N | Y | P |
| Reiss, 2015 | Y | N | Y | Y | Y | Y | Y | N | N | Y | U | Y | Y | Y | Y | Y | N | N | Y | N |
| Willekens, 2015 | Y | N | N | U | Y | Y | Y | N | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Sharma, 2015 | Y | N | N | Y | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Meyer, 2015 | Y | N | Y | U | N | N | Y | N | N | N | U | Y | Y | U | U | Y | N | Y | Y | N |
| Warrow, 2015 | Y | N | Y | Y | Y | Y | Y | Y | N | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Dyer, 2015 | Y | N | U | Y | P | N | Y | N | N | P | U | Y | Y | U | Y | Y | Y | N | Y | N |
| Zhao, 2015 | Y | N | U | U | N | N | Y | Y | N | N | U | Y | Y | Y | U | Y | Y | Y | Y | N |
| Coskey, 2014 | Y | N | Y | N | N | N | Y | N | N | N | U | Y | Y | U | U | Y | N | Y | Y | N |
| Steinle, 2014 | Y | N | U | Y | Y | N | Y | N | N | P | U | Y | Y | U | Y | Y | N | Y | Y | N |
| Roth, 2014 | Y | N | U | U | N | N | Y | Y | N | N | U | Y | U | U | Y | N | N | N | Y | N |
| Singh, 2014 | Y | N | Y | U | Y | Y | Y | Y | N | Y | U | Y | Y | U | Y | Y | N | Y | Y | P |
| Kim, 2013 | Y | N | N | N | N | N | Y | N | N | N | U | Y | U | U | U | Y | N | N | Y | N |

Green color represents for rating of “yes (Y)”. Yellow color represents for rating of “partial (P)/unclear (N)”. Red color represents for rating of “no (N)”.

**Supplementary Table 9. Publication bias assessment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Egger’s Test | |  | Begg’ Test | |
|  | t | *p* |  | Z | *p* |
| RCTs |  |  |  |  |  |
| VMA release | 1.42 | 0.29 |  | -0.34 | 1.00 |
| MH closure | - | - |  | 0.00 | 1.00 |
| Vision improvement | 2.00 | 0.30 |  | 0.00 | 1.00 |
| Incidence of vitrectomy | -5.03 | 0.13 |  | 1.04 | 0.30 |
| Incidence of all AEs | 0.97 | 0.40 |  | 0.24 | 0.81 |
| Incidence of any serious AE | - | - |  | 0.00 | 1.00 |
| Incidence of all ocular AE | 1.68 | 0.19 |  | 0.73 | 0.46 |
| Incidence of any serious ocular AEs | 0.80 | 0.51 |  | -0.34 | 1.00 |
| Cohort studies |  |  |  |  |  |
| Proportion of VMA release | 0.25 | 0.81 |  | 1.23 | 0.22 |
| Proportion of MH closure | 1.09 | 0.29 |  | 1.82 | 0.07 |
| Proportion of ≥ 2-line improvement in BCVA | 1.99 | 0.12 |  | 0.38 | 0.71 |
| Mean changes of logMAR in BCVA | -0.37 | 0.72 |  | 0.12 | 0.90 |

Abbreviations: VMA, vitreomacular adhesion; MH, macular hole; AEs, adverse events; BCVA, best-corrected visual acuity

**Supplementary File 1. Searching strategy and result**

**Number of citations by each database searched**

|  |  |
| --- | --- |
| **Databases** | **Citations** |
| PubMed | 624 |
| EMBASE | 483 |
| Cochrane Library | 77 |
| Total databases | 1184 (with 235 duplicates) |
| Total databases after removing duplicates | 949 |

**Searching strategy for PubMed**

1. "vitreous body" [MeSH Terms]
2. "vitreous detachment" [MeSH Terms]
3. "retinal perforations" [MeSH Terms]
4. "tissue adhesions" [MeSH Terms]
5. vitreomacular adhesion [Title/Abstract]
6. vitreomacular traction [Title/Abstract]
7. macula hole [Title/Abstract]
8. VMA [Title/Abstract]
9. VMT [Title/Abstract]
10. MH [Title/Abstract]
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12. "fibrinolysin" [MeSH Terms]
13. "fibrinolytic agents" [MeSH Terms]
14. "proteolysis" [MeSH Terms]
15. "peptide fragments" [MeSH Terms]
16. ocriplasmin [Title/Abstract]
17. Jetrea [Title/Abstract]
18. Microplasmin [Title/Abstract]
19. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
20. 11 AND 19

**Search strategy for EMBASE**

1. 'vitreous body'/exp/mj
2. 'vitreous detachment'/exp/mj
3. 'retinal perforations'/exp/mj
4. 'tissue adhesions'/exp/mj
5. 'vitreomacular adhesion':ab,ti
6. 'vitreomacular traction':ab,ti
7. 'macula hole':ab,ti
8. 'VMA':ab,ti
9. 'VMT':ab,ti
10. 'MH':ab,ti
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12. 'fibrinolysin'/exp/mj
13. 'fibrinolytic agents'/exp/mj
14. 'proteolysis'/exp/mj
15. 'peptide fragment'/exp/mj
16. 'ocriplasmin':ab,ti
17. 'Jetrea':ab,ti
18. 'Microplasmin':ab,ti
19. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
20. 11 AND 19

**Search strategy for Cochrane Library**

1. Mesh Descriptor: [vitreous body] explode all trees
2. Mesh Descriptor: [vitreous detachment] explode all trees
3. Mesh Descriptor: [retinal perforations] explode all trees
4. Mesh Descriptor: [tissue adhesions] explode all trees
5. (vitreomacular adhesion) :ti,ab,kw
6. (vitreomacular traction) :ti,ab,kw
7. (macula hole) :ti,ab,kw
8. (VMA) :ti,ab,kw
9. (VMT) :ti,ab,kw
10. (MH) :ti,ab,kw
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12. Mesh Descriptor: [fibrinolysin] explode all trees
13. Mesh Descriptor: [fibrinolytic agents] explode all trees
14. Mesh Descriptor: [proteolysis] explode all trees
15. Mesh Descriptor: [peptide fragment] explode all trees
16. (ocriplasmin) :ti,ab,kw
17. (Jetrea) :ti,ab,kw
18. (Microplasmin) :ti,ab,kw
19. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
20. 11 AND 19

**Supplementary File 2. References to studies included in this review**

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