**Supplemental online material**

**Comparative efficacy of bevacizumab, ranibizumab, and aflibercept for treatment of macular edema secondary to retinal vein occlusion: A systematic review and network meta-analysis**

**Table S1.** Search strategy in Embase.

|  |  |  |
| --- | --- | --- |
| **No.** | **Search** | **Results** |
| 1 | (retina\* and vein\* and (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or embolism\*)).af. | 10030 |
| 2 | (RVO or CRVO or CVO or BRVO).af. | 3458 |
| 3 | 1 or 2 | 11017 |
| 4 | (bevacizumab or avastin).af. | 48849 |
| 5 | (ranibizumab or lucentis).af. | 7621 |
| 6 | (aflibercept or eylea).af. | 4201 |
| 7 | (anti?vascular endothelial growth factor\* or anti?vegf\* or vascular endothelial growth factor inhibit\* or vegf inhibit\*).af. | 3303 |
| 8 | (anti?angiogen\* or angiogenesis inhibit\*).af. | 41678 |
| 9 | intravitreal\*.af. | 24635 |
| 10 | 4 or 5 or 6 or 7 or 8 | 87172 |
| 11 | 3 and 10 | 1732 |
| 12 | 3 and 9 and 10 | 1362 |
| 13 | 11 and "Article" [Publication Type] | 985 |
| 14 | 13 and "clinical trial" [Subjects] | 106 |

**Table S2.** Reasons for exclusion.

|  |  |  |
| --- | --- | --- |
| **REASONS** | | **Number** |
| **Excluded at title and abstract screening** | | **245** |
|  | *- not patients with RVO* | *29* |
|  | *- not interventions of interest* | *76* |
|  | *- no comparator* | *65* |
|  | *- not outcomes of interest* | *24* |
|  | *- not RCT* | *18* |
|  | *- published in non-English* | *12* |
|  | *- preliminary results presented as conference abstract* | *21* |
| **Could not retrieve full-text articles** | | **2** |
| **Excluded at full-text screening: not RCT** | | **2** |
| **Total excluded articles** | | **249** |

**Table S3.** Study included in the systematic review.

| **Study** | **Study design** | **Key inclusion criteria** | | | | **Treatment regimen** | **patients completed study at 6 months** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **History of anti-VEGF treatment** | **BCVA** | **CMT (μm)** | **Disease duration** |
| SCORE2 [2017] | double-blinded RCT | Prior intravitreal anti–VEGF use was allowed if it was more than 2 months before randomization | E-ETDRS VA letter score (VALS) between 19 and 73 (possible range is 0 to 100 letters, higher scores indicate better VA) | ≥ 300 or 320 (depends on measuring machine) | -- | 1) month 0-5: IVB monthly injection, month 6-8: good respond patients were re-randomized to IVB monthly or treat and extend schedule while poor responders received IVA for 3 months follow by IVA monthly PRN 2) month0-5: IVA monthly injection, month 6-8: good respond patients were re-randomized to IVB monthly or treat and extend schedule while poor responders received dexamethasone implant for 1 months follow by dexamethasone implant monthly PRN | 1) IVB 95.1%  2) IVA 97.2% |
| Lucatto et al [2017] | double-blinded RCT | anti-VEGF naïve | BCVA ≤ 20/40 | ≥ 250 | -- | 1) IVB monthly injection for 6 months follow by IVB monthly PRN until month 12 (if BCVA ≤ 20/40 or CFT ≥ 250) 2) IVTA at month 0 and 4 and sham at month 1, 2, 3, 5 | 1) IVB 78.6% 2) IVTA 81.8%  3) Sham 80% |
| GALILEO [2013, 2014, 2014] | double-blinded RCT | anti-VEGF naïve | ETDRS BCVA of 20/40 to 20/320 (73 to 24 letters | ≥ 250 | ≤ 9 months | 1) week 0-20: IVA q 4 weeks, week 24-48: IVA PRN or sham q 4 weeks, week 52-72: IVA PRN q 8 weeks 2) week 0-20: Sham q 4 weeks, week 24-48: sham q 4 weeks, week 52-72: IVA PRN q 8 weeks | 1) IVA 90.6% 2) Sham 78.9% |
| COPERNICUS [2012, 2013, 2014] | double-blinded RCT | anti-VEGF naïve | ETDRS BCVA of 20/40 to 20/320 (73 to 24 letters) in the study eye | ≥ 250 | ≤ 9 months | 1) week 0-24: IVA q 4 weeks, week 24-52: IVA PRN or sham q 4 weeks, week 52-100: IVA PRN or sham q 8 weeks 2) week 0-24: sham q 4 weeks, week 24-52: IVA PRN or sham q 4 weeks, week 52-100: IVA PRN or sham q 8 weeks | 1) IVA 95.7% 2) Sham 81.1% |
| Epstein [2012, 2012] | double-blinded RCT | anti-VEGF naïve | BCVA 15 to 65 ETDRS letters (Snellen equivalent approximately 20/50 to 20/500) | ≥ 300 | ≤ 6 months | 1) week 0-20: IVB q 6 weeks, week 24-44: IVB q 6 weeks 2) week 0-20: sham q 6 weeks, week 24-44: IVB q 6 weeks | 1) IVB 100% 2) Sham 100% |
| CRUISE [2010, 2011] | double-blinded RCT | Excluded: Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 months before day 0 | BCVA using ETDRS charts of 20/40 to 20/320 (Snellen equivalent) | ≥ 250 | ≤ 12 months | 1) month 0-5: IVR monthly injection, month 6-11: IVR monthly PRN 2) month 0-5: IVR monthly injection, month 6-11: IVR monthly PRN 3) month 0-5: sham monthly injection, month 6-11: 0.5 mg IVR monthly PRN | 1) IVR(0.3) 97.7% 2) IVR(0.5) 91.5% 3) Sham 88.5% |
| ROCC [2010] | double-blinded RCT | anti-VEGF naïve (excluded: Prior treatment of macular disease) | BCVA between ≤ 73 and ≥ 6 letters using an ETDRS chart | have a macular edema verified by OCT | ≤ 6 months | 1) IVR monthly injection for 3 months, followed by reinjection if edema presents until month 6 2) sham monthly injection for 3 months, followed by reinjection if edema presents until month 6 | 1) IVR(0.5) 93.8%  2) Sham 87.5% |
| Khan et al [2017] | open-label RCT | anti-VEGF naïve | vision of LogMAR 0.3 or worse | ≥ 250 | presenting within one month of onset of symptoms | 1) IVB monthly PRN from month 0 to 12 2) IVB monthly PRN from month 4 to 12 | 1) IVB (prompt) 100% 2) IVB (deferred) 100% |
| MARVEL [2015] | double-blinded RCT | Excluded: Prior anti-VEGF treatment in the study eye | BCVA of 20/40 to 20/320 (73 to 24 letters) | ≥ 250 | < 9 months | 1) IVB at baseline, follow by monthly PRN from months 1-6 2) IVR at baseline, follow by monthly PRN from months 1-6 | 1) IVB 89.5% 2) IVR(0.5) 89.2% |
| Moradian et al [2011] | double-blinded RCT | -- | BCVA ≤ 20/50  (excluded: BCVA ≥ 20/40) | ≥ 250 | -- | 1) IVB injection at week 0 and 6 2) sham injection at week 0 and 6 | -- |
| BRAVO [2010, 2011] | double-blinded RCT | Excluded: Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 months before day 0 | BCVA using ETDRS charts of 20/40 to 20/400 (Snellen equivalent) | ≥ 250 | ≤ 12 months | 1) month 0-5: IVR monthly injection, month 6-11: IVR monthly PRN 2) month 0-5: IVR monthly injection, month 6-11: IVR monthly PRN 3) month 0-5: sham monthly injection, month 6-11: 0.5 mg IVR monthly PRN | 1) IVR(0.3) 95.5% 2) IVR(0.5) 95.4% 3) Sham 93.2% |
| **Abbreviations**: anti-VEGF, anti-vascular endothelial growth factors; BCVA, best corrected visual acuity; CMT, central macular thickness; RCT, randomized controlled trials; ETDRS, early treatment diabetic retinopathy study; VA, visual acuity; IVB, intravitreal bevacizumab; IVA, intravitreal aflibercept; PRN, pro re nata; BCVA, best-corrected visual acuity; IVTA, intravitreal triamcinolone acetate; IVR, intravitreal ranibizumab; OCT, optical coherence tomography; LogMAR, logarithm of minimum angle of resolution. | | | | | | |  |

**Table S4.** Authors' judgments about each risk of bias domain for each included study using the Risk of bias 2.0 assessment.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Randomization process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported result** | **Overall Bias** |
| SCORE2 (2017) | Low | Low | Low | Low | Low | **Low** |
| Lucatto et al (2017) | Low | Low | Low | Low | Low | **Low** |
| GALILEO (2013) | Low | Low | Low | Low | Low | **Low** |
| COPERNICUS (2012) | Low | Low | Low | Low | Low | **Low** |
| Epstein et al (2012) | Low | Low | Low | Low | Low | **Low** |
| CRUISE (2010) | Low | Low | Low | Low | Low | **Low** |
| ROCC (2010) | Low | Low | Some concerns | Low | Low | **Some concerns** |
| Khan et al (2017) | High | Low | Low | High | Low | **High** |
| MARVEL (2015) | Low | Low | Low | Low | Low | **Some concerns** |
| Moradian et al (2011) | Low | Low | Some concerns | Low | Low | **Some concerns** |
| BRAVO (2010) | Low | Low | Low | Low | Low | **Low** |

**Table S5.** The number needed to treat for gaining at least 15 letters after 6 months of follow-up.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Intervention  (reference) [n/N]** | | **Comparator [n/N]** | | **NNT**  **to benefit** |
| SCORE2**[13]** | IVB | [106/182] | IVA | [114/180] | 20 |
| GALILEO**[21, 22, 23]** | Sham | [15/68] | IVA | [62/104] | 3**a** |
| COPERNICUS**[26, 27, 28]** | Sham | [9/73] | IVA | [64/114] | 2**a** |
| Epstein et al**[32, 33]** | Sham | [6/30] | IVB | [18/30] | 3 |
| CRUISE**[24, 25]** | Sham | [22/130] | IVR(0.5) | [62/130] | 3**a** |
| Sham | [22/130] | IVR(0.3) | [61/132] | 3**a** |
| IVR(0.3) | [61/132] | IVR(0.5) | [62/130] | 68 |
| MARVEL**[31]** | IVB | [22/38] | IVR(0.5) | [22/37] | 64 |
| BRAVO**[29, 30]** | Sham | [38/132] | IVR(0.5) | [80/131] | 3**a** |
| Sham | [38/132] | IVR(0.3) | [74/134] | 4**a** |
| IVR(0.3) | [74/134] | IVR(0.5) | [80/131] | 17 |
| **Abbreviations**: n, number of patients who gained at least 15 ETDRS letters after 6 months of follow-up; N, total number of patients; NNT, Number needed to treat; IVB, intravitreal bevacizumab; IVA, intravitreal aflibercept; IVR(0.5), intravitreal ranibizumab 0.5 mg; IVR(0.3), intravitreal ranibizumab 0.3 mg. **a**The proportions of patients who gained at least 15 RTDRS letters between groups were statistically significant difference. | | | | | |

**Table S6.** Node-splitting to assess consistency between direct and indirect evidence.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Comparison** | **Direct evidence** | |  | **Indirect evidence** | |  | **Difference between direct and indirect** | | **P-value** |
| **Coef.** | **SE** |  | **Coef.** | **SE** |  | **Coef.** | **SE** |
| **A) Proportion of patients gained ≥ 15 letters at 6 months** | IVA vs Sham | -1.19 | 0.21 |  | -0.99 | 0.26 |  | -0.20 | 0.32 | 0.534 |
| IVA vs IVB | -0.08 | 0.12 |  | -0.28 | 0.30 |  | 0.20 | 0.32 | 0.535 |
| IVB vs Sham | -1.10 | 0.40 |  | -0.97 | 0.17 |  | -0.12 | 0.43 | 0.775 |
| IVB vs IVR | 0.03 | 0.19 |  | -0.25 | 0.23 |  | 0.28 | 0.30 | 0.353 |
| IVR vs Sham | -0.85 | 0.13 |  | -1.12 | 0.27 |  | 0.28 | 0.30 | 0.353 |
| **B) Mean change in BCVA at 6 months from baseline** | IVA vs Sham | -17.71 | 2.34 |  | -12.70 | 4.78 |  | -5.01 | 5.30 | 0.345 |
| IVA vs IVB | -0.27 | 2.99 |  | -5.28 | 4.38 |  | 5.01 | 5.30 | 0.345 |
| IVB vs Sham | -16.10 | 6.02 |  | -14.49 | 3.20 |  | -1.61 | 6.81 | 0.813 |
| IVB vs IVR | 2.50 | 4.15 |  | -4.54 | 3.56 |  | 7.04 | 5.47 | 0.198 |
| IVR vs Sham | -12.51 | 1.90 |  | -19.55 | 5.13 |  | 7.04 | 5.47 | 0.198 |
| **C) Mean change in CMT at 6 months from baseline** | IVA vs Sham | 295.77 | 119.06 |  | 421.65 | 212.76 |  | -125.88 | 243.81 | 0.606 |
| IVA vs IVB | 38.00 | 166.05 |  | -88.06 | 178.57 |  | 126.06 | 243.85 | 0.605 |
| IVB vs Sham | 324.00 | 181.13 |  | 361.00 | 147.81 |  | -37.00 | 233.78 | 0.874 |
| IVB vs IVR | 24.58 | 169.82 |  | -143.69 | 159.61 |  | 168.27 | 233.06 | 0.470 |
| IVR vs Sham | 439.16 | 95.08 |  | 270.80 | 212.68 |  | 168.36 | 233.02 | 0.470 |

**Abbreviations**: BCVA, best-corrected visual acuity; CMT, central macular thickness; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; Sham, Sham injection; vs, versus; Coef., coefficient; SE, standard error.

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**Figure S1.** Network forest plot summarizing effect size by study and by treatment**.**



**Figure S2.** Interval plot illustrating effect size and 95% confidence interval of efficacy outcomes.



**Figure S3.** Funnel plots to check for publication bias in network meta-analysis.