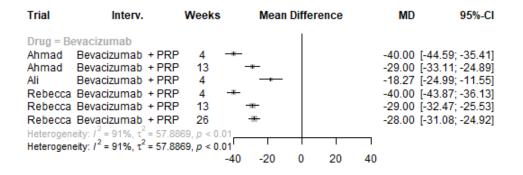
AVID: Complete results of all published data analyses for outcomes other than BCVA

This document presents tables and figures for all analyses, using data from publications of included RCTs for outcomes other than BCVA. These mostly consist of forest plots without meta-analysis, because the evidence was generally too limited in extent, and too diverse in intervention and follow-up times, to justify a full meta-analysis.

As meta-analysis was not possible for most outcomes the forest plots without meta-analysis include trials of proliferative and non-proliferative retinopathy, to aid comparison.

1 FOREST PLOTS OF OUTCOMES WITHOUT META-ANALYSIS

These forest plots show results for all anti-VEGF types, and at all follow-up times. Note that this means some trials appear more than once in a forest plot.



NVD (neovascularization of the disc)

Figure 1 Forest plot of all NVD data (left side favours anti-VEGF)

NVE (neovascularization elsewhere)

| Trial | Interv. | Weeks | Mean Difference | MD | 95%-CI |
|---|---|--------------------------|-----------------------|--|--|
| Ahmad Ahmad Ali Rebecca Rebecca Rebecca | Bevacizumab + PRP | 13 4 4 13 26 | * * * * * | -1.25 [-1 -1.64 [-2 -2.15 [-2 -1.25 [-1 | 1.73; -0.77] 1.65; -0.85] 2.26; -1.02] 2.56; -1.74] 1.59; -0.91] 1.76; -1.04] |
| PRIDE PRIDE PRIDE PRIDE PROTEUS Heterogene | nibuzimab Ranibizumab + PRP Ranibizumab + PRP Ranibizumab + PRP 8 Ranibizumab + PRP 9 Ranibizumab + PRP ity: $l^2 = 14\%$, $\tau^2 = < 0.000$ ity: $l^2 = 50\%$, $\tau^2 = 0.0789$ | 12 1, p = 0.33 | | -1.94 [-3 -3.66 [-3 -0.80 [-2 | 9.43; -0.85] 3.51; -0.37] 7.63; 0.31] 2.43; 0.83] 2.90; -0.58] |

Figure 2 Forest plot of all NVE data (left side favours anti-VEGF)

Diabetic Macular Oedema (DME)

| Trial | Interv. | Weeks | Risk Ratio | RR 95%-CI |
|--|---|---------------------------------------|-------------------|--|
| Drug = Afliberce CLARITY PANORAMA PANORAMA PANORAMA PANORAMA PROTOCOL W Heterogeneity: J ² | Aflibercept Aflibercept 2q16 Aflibercept 2q8 Aflibercept 2q8 Aflibercept 2q8 Aflibercept 2q8 Aflibercept 2q8 aflibercept 2q8 | 52 — 52 52 100 100 104 | | 0.21 [0.01; 4.23] 0.24 [0.12; 0.47] 0.34 [0.18; 0.63] 0.28 [0.17; 0.49] 0.43 [0.27; 0.69] 0.28 [0.12; 0.63] |
| PROTEUS PROTOCOL S Heterogeneity: / ² | mab Ranibizumab Ranibizumab + PRP Ranibizumab + PRP Ranibizumab = 0%, τ^2 = 0, p = 0.72 = 0%, τ^2 = 0, p = 0.91 | | | 0.22 [0.05; 0.96] 0.54 [0.20; 1.45] 0.21 [0.01; 4.34] 0.31 [0.18; 0.55] |

Figure 3 Forest plot of DME incidence (left side favours anti-VEGF)

Improvement in diabetic retinopathy severity score (DRSS)

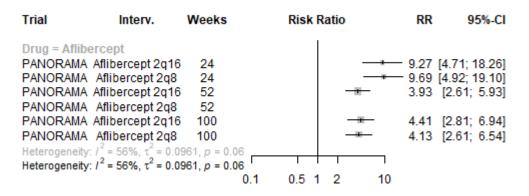


Figure 4 Forest plot of improvement in DRSS severity (right side favours anti-VEGF)

Proliferative retinopathy incidence

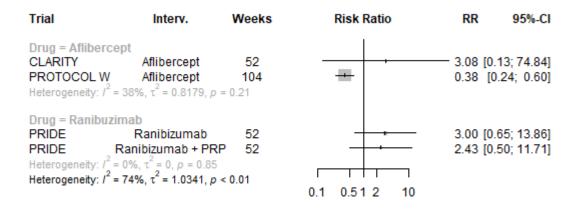


Figure 5 Forest plot of proliferative DR (left side favours anti-VEGF)

Regressive neovascularisation

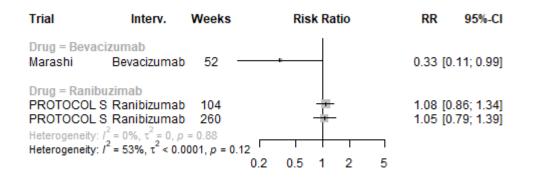


Figure 6 Forest plot of regressive neovascularisation (left side favours anti-VEGF)

Use of other treatments

| Trial | Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|--|---|----------------------|----------------|----|--------------------------|
| Drug = Aflibero PANORAMA Af PANORAMA A Heterogeneity: / Heterogeneity: / | libercept 2q10 flibercept 2q8 = 0%, τ ² = 0, ρ | 100 = 0.88 | 0.1 0.5 1 2 10 | - | .03; 0.55] .03; 0.64] |

Figure 7 Forest plot of use of other treatments (left side favours anti-VEGF)

Vitrectomy

| Trial | Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|---|--|--------------------------|---------------|--------------|---|
| Drug = Aflibercept CLARITY PROTOCOL W Heterogeneity: / ² = 0% | Aflibercept Aflibercept 6, $\tau^2 = 0$, $p = 0.68$ | 52 104 | | | [0.02; 1.17] [0.01; 8.09] |
| PROTEUS Rai PROTOCOL S | hibizumab + PRP hibizumab + PRP Ranibizumab Ranibizumab $\%, \tau^2 = 0.2139, p =$ | 52 104 260 0.14 | 0.1 0.51 2 10 | 2.15 0.28 | [0.26; 8.21] [0.20; 22.79] [0.13; 0.59] [0.35; 0.94] |

Figure 8 Forest plot of vitrectomy incidence (left side favours anti-VEGF)

Vitreous haemorrhage

| Trial | Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|---|--|--------------------|---------------|--|--|
| Drug = Aflibercept CLARITY PROTOCOL W Heterogeneity: / ² = 09 | Aflibercept Aflibercept 6, $\tau^2 = 0$, $p = 0.37$ | 52 104 | | | 0.24; 0.99] 0.25; 3.92] |
| PRIDE PRIDE Rai PROTEUS Rai PROTOCOL S | Ranibizumab Ranibizumab nibizumab + PRF nibizumab + PRF Ranibizumab Ranibizumab | 2 52 104 260 | | 1.00 [0 0.97 [0 1.31 [0.79 [| 0.16; 1.38] 0.07; 15.36] 0.06; 14.94] 0.61; 2.84] 0.59; 1.05] 0.84; 1.28] |
| Drug = Bevacizuma Marashi Heterogeneity: / ² = 49 | Beyacizumab | 52 0.40 | 0.1 0.51 2 10 | — 3.00 [0 | .13; 68.09] |

Figure 9 Forest plot of vitreous haemorrhage incidence (left side favours anti-VEGF)

2 ADVERSE EVENT OUTCOMES

These forest plots show results for all anti-VEGF types, and at all follow-up times. Note that this means some trials appear more than once in a forest plot. For simplicity, only adverse event outcomes reported in two or more studies are presented.

Cataracts

| Trial | Interv. | Weeks | | Risk Rat | io | RR | 95%-CI |
|-------------------|--|----------|--------|----------|----|------|----------------|
| CLARITY | Aflibercept | 52 | | • | | 0.33 | [0.01; 8.10] |
| Ferraz PROTEUS | Ranibizumab Ranibizumab + PRP | 26 52 | | | | 5.36 | [0.27; 108.42] |
| PROTOCOL S | Ranibizumab | 104 | | ÷. | | 0.87 | [0.56; 1.33] |
| PROTOCOL W | Aflibercept ² = 0%, τ ² < 0.0001, p = 0 | 104 | | | | | |
| neterogeneity. I | - 0%, c < 0.0001, p = 0 | | 01 0.1 | 1 | 10 | 100 | |

Figure 10 Forest plot of cataracts data (left side favours anti-VEGF)

Conjunctival haemorrhage

| Trial | Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|----------|--|-------|---------------|------|--|
| PANORAMA | Aflibercept Aflibercept 2q16 Aflibercept 2q8 $I^2 = 0\%, \tau^2 = 0, p$ | 100 | 0.1 0.51 2 10 | 2.01 | 0.12; 72.89] [0.91; 4.44] [1.55; 6.93] |

Figure 11 Forest plot of conjunctival haemorrhage data (left side favours anti-VEGF)

Cardiovascular mortality

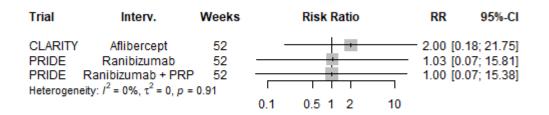


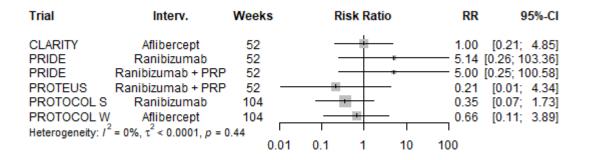
Figure 12 Forest plot of cardiovascular mortality data (left side favours anti-VEGF)

Death (all-cause mortality)

| Trial Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|---|----------------------|------------|-----------|--|
| PRIDERanibizumabPRIDERanibizumab + PRPSao Paulo ARanibizumab + PRP (PASCAL)Sao Paulo BRanibizumab + PRPHeterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.88$ | 52 52 48 48 | | 2.00 [0.1 | 07; 15.81] 19; 21.09] 12; 63.52] |

Figure 13 Forest plot of death data (left side favours anti-VEGF)

Myocardial infarction



Ocular pain

| Trial | Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|--|--|-------|---------------|----------------------|--|
| CLARITY PANORAMA PANORAMA PRIDE PRIDE Heterogeneity | Aflibercept Aflibercept 2q16 Aflibercept 2q8 Ranibizumab Ranibizumab + PRP $t^2 = 20\%, \tau^2 < 0.0001, t^2$ | | | 1.64 0.87 4.11 | [0.43; 5.18] [0.63; 4.28] [0.27; 2.77] [0.48; 35.02] [1.35; 74.12] |
| | | | 0.1 0.51 2 10 | | |

Figure 14 Forest plot of ocular pain data (left side favours anti-VEGF)

Raised intraocular pressure

| Trial | Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|---|---|-----------|---------------|--------|------------------------------|
| CLARITY Ferraz | Aflibercept Ranibizumab | 52 26 | | - 3.00 | [0. <mark>1</mark> 2; 72.89] |
| PROTEUS PROTOCOL S Heterogeneity: | Ranibizumab + PRP S Ranibizumab $r^2 = 0\%, \tau^2 = 0, p = 0.75$ | 52 104 | 0.1 0.51 2 10 | | [0.19; 3.38] [0.57; 1.38] |

Figure 15 Forest plot of raised intraocular pressure data (left side favours anti-VEGF)

Retinal detachment

| Trial | Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|--|---------|----------------------------|---------------|---------|--|
| CLARITY PROTEUS PROTOCOL S PROTOCOL W Heterogeneity: / | | 52 — 52 — 104 104 | 0.1 0.51 2 10 | 0.43 [0 | .01; 4.34] .22; 0.81] .14; 6.94] |

Figure 16 Forest plot of retinal detachment data (left side favours anti-VEGF)

Retinal tear

| Trial | Interv. | Weeks | Risk Ratio | RR | 95%-CI |
|---|--|-----------|---------------|-----------|--------------|
| CLARITY | Aflibercept | 52 | | - 3.00 [0 | .12; 72.89] |
| PROTEUS PROTOCOL S Heterogeneity: / | Ranibizumab + PRP Ranibizumab $^{2} = 0\%, \tau^{2} = 0, p = 0.98$ | 52 104 | r | - 3.19 [0 |).13; 77.78] |
| | | | 0.1 0.51 2 10 | | |

Figure 17 Forest plot of retinal data (left side favours anti-VEGF)

Serious adverse event (SAE, however defined)

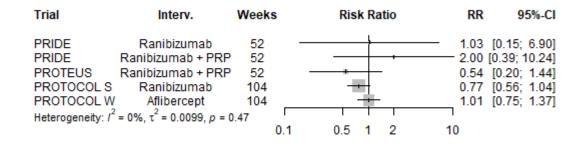


Figure 18 Forest plot of SAE data (left side favours anti-VEGF)

Stroke

| Trial | Interv. | Weeks | s | R | lisk Rat | io | I | RR | 9 | 5%-CI |
|---|---|------------------------|------|-----|----------|----|----------|----|---|-----------------|
| CLARITY PROTEUS PROTOCOL S PROTOCOL W Heterogeneity: 1 ² | Aflibercept Ranibizumab + PRP Ranibizumab Aflibercept $r^2 = 0\%, \tau^2 = 0, p = 0.49$ | 52 52 104 104 | 0.01 | 0.1 | + | | 3. 0. | | [0.37; 13 [0.13; 7 [0.20; [0.20; | 76.78] 2.47] |

Figure 19 Forest plot of stroke data (left side favours anti-VEGF)

3 META-ANALYSES OF OTHER OUTCOMES AND ADVERSE EVENTS

All meta-analyses presented assumed that the impact of anti-VEGF on outcome (or adverse event) is the same for all types of anti-VEGF (in isolation or combined with PRP), and at all follow-up times. For trials with multiple time points, the longest follow-up was used. For trial with multiple arms only one anti-VEGF arm was used; arms using anti-VEGF alone were preferred.

NVE

| Trial | Interv. | Mean Difference | MD | 95%-CI Weight |
|---|---------|--------------------------|------------------------|--|
| Drug = Bevacizumab Ahmad Ali Rebecca Random effects mode Heterogeneity: $I^2 = 0\%$, τ^2 | | * * * | -1.64 [-2 -1.40 [-1 | .65; -0.85] 36.1% .26; -1.02] 15.0% .76; -1.04] 44.2% .63; -1.13] 95.4% |
| Drug = Ranibuzimab PRIDE PROTEUS Random effects mode Heterogeneity: $I^2 = 0\%$, τ^2 | | | -1.74 [-2 | .63; 0.31] 0.4% .90; -0.58] 4.3% .01; -0.78] 4.6% |
| Random effects mode Heterogeneity: $l^2 = 0\%$, τ^2 Test for subgroup differen | - | 3) -4 -2 0 2 4 6 | -1.40 [-1. | .65; -1.16] 100.0% |

Figure 20 Meta-analysis of NVE (left side favours anti-VEGF)

NVD

| Trial | Interv. | Mean Difference | MD | 95%-Cl Weight |
|--|---|-----------------------|--------------|---|
| Ahmad Ali PRIDE PROTEUS Rebecca | Bevacizumab + PRF Bevacizumab + PRF Ranibizumab Ranibizumab + PRF Bevacizumab + PRF | | -18.27 [-24. | 11; -24.89] 34.9% 99; -11.55] 27.5% 0.0% 0.0% 08; -24.92] 37.6% |
| Random effects mo Heterogeneity: 1 ² = 74% | del δ, τ ² = 22.6512, <i>p</i> = 0.02 | -30 -20 -10 0 10 20 3 | _ | 70; -19.65] 100.0% |

Figure 21 Meta-analysis of NVD (left side favours anti-VEGF)

Other non-vison outcomes

This forest plot shows the summary results of each meta-analysis (each bar is a meta-analysis result). Meta-analyses are restricted to trials of proliferative retinopathy. Full forest plots for each outcome are not presented.

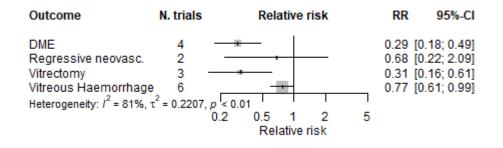


Figure 22 Meta-analysis summary for non-vision outcomes in PDR trials (left side favours anti-VEGF)

Adverse events

This forest plot shows the summary results of each meta-analysis (each bar is a meta-analysis result). Meta-analyses are restricted to trials of proliferative retinopathy. Full forest plots for each outcome are not presented.

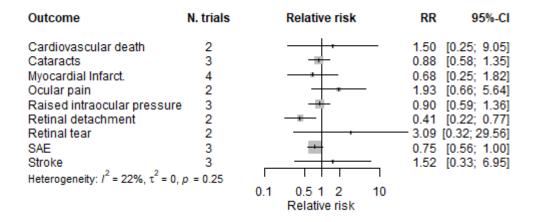


Figure 23 Meta-analysis summary for adverse events (left side favours anti-VEGF)

Diabetic macular oedema in non-proliferative retinopathy

DME was the only outcome other than BCVA reported in both trials of NPDR.

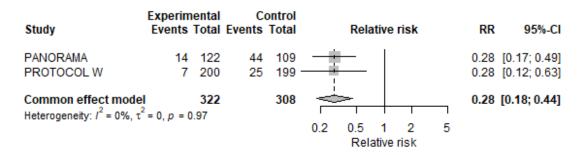


Figure 24 DME incidence in NPDR trials