Hemiretinal vein occlusion 12-month outcomes are unique with vascular endothelial growth factor inhibitors: data from the Fight Retinal Blindness! Registry

Adrian Robert Hunt,1,2 Vuong Nguyen,1 Jennifer J Arnold,3 Ian L McAllister,4 Hemal Mehta,1,5 Alessandro Invernizzi,4,6 Theodorus Ponsioen,7 Pierre-Henry Gabrielle,1,8 Louise O’Toole,9 Pavol Kusenda,10 Socorro Alforja,11 Daniel Barthelmes,1,12 Mark C Gillies1

ABSTRACT

Background/aims To describe baseline characteristics and 12-month outcomes with vascular endothelial growth factor (VEGF) inhibitors of treatment-naïve hemiretinal vein occlusion (HRVO) compared with branch (BRVO) and central (CRVO) variants in routine clinical care.

Methods A database observational study recruited 79 HRVO eyes, 590 BRVO eyes and 344 CRVO eyes that initiated therapy over 10 years. The primary outcome was mean change in visual acuity (VA—letters read on a logarithm of minimal angle of resolution chart) at 12 months. Secondary outcomes included mean change in central subfield thickness (CST), injections and visits.

Results At baseline, mean VA in HRVO (53.8) was similar to CRVO (51.9; p=0.40) but lower than BRVO (59.4; p=0.009). HRVO eyes improved to match BRVO eyes from soon after treatment started through 12 months. Mean change in VA was greater in HRVO (+16.4) than both BRVO (+11.4; p=0.006) and CRVO (+8.5; p=0.001). Mean change in CST in HRVO (−231 µm) was similar to CRVO (−259 µm; p=0.33) but greater than BRVO eyes (−151 µm; p=0.003). The groups had similar median burdens of eight injections and nine visits.

Conclusions HRVO generally experienced the greatest mean change in VA of the three types of RVO when treated with VEGF inhibitors, ending with similar 12-month VA and CST to BRVO despite starting closer to CRVO. Inclusion of HRVO in BRVO or CRVO cohorts of clinical trials would be expected to proportionally inflate and skew the visual and anatomic outcomes.

INTRODUCTION

Hemiretinal vein occlusion (HRVO) is regarded pathologically as a type of central RVO (CRVO) with a better prognosis.1–3 For many years, it was managed like branch RVO (BRVO) with laser.4 It remains unclear in the era of intravitreal injections whether HRVO should be regarded as a BRVO, CRVO or as a separate entity.

The last time that treatment response of HRVO was differentiated from BRVO and CRVO was in Report 14 of the SCORE study using triamcinolone as the comparator. The study suffered from a lack of power and modest response to treatment but at 12 months the thirty HRVO eyes did achieve the greatest improvement in visual acuity (VA) (+8.8 letters), followed by BRVO (+4.5 letters) and CRVO (−1.4 letters).5

Trials regarding vascular endothelial growth factors (VEGF) inhibitors have variably included HRVO eyes. After the SCORE group included HRVO with BRVO when investigating triamcinolone, they later included HRVO with CRVO in SCORE2 reporting noninferiority of bevacizumab compared with aflibercept.6 The pivotal trials investigating safety and efficacy of VEGF inhibitors in RVO excluded HRVO from CRVO but instead included HRVO in BRVO cohorts receiving ranibizumab (16%–17% HRVO) or aflibercept (undisclosed proportion).7–9 Just last year (2020), Vader et al reported non-inferiority of bevacizumab and ranibizumab in RVO with a subgroup analysis that combined 47 HRVO eyes with 97 CRVO eyes.10

To support that choice the authors cited a review article which argued HRVO was a variant of CRVO, with similar pathogenesis and risk factors.11 Grouping with BRVO or CRVO has resulted in a lack of evidence specific to HRVO and at the same time made the practice difficult to justify. Here, we have compared the outcomes with VEGF inhibitors of a large number of treatment naïve eyes with HRVO, BRVO and CRVO in routine clinical practice in order to establish whether HRVO is similar to BRVO or CRVO or whether it has distinct outcomes.

MATERIALS AND METHODS

Design and setting This study adhered to the tenets of the Declaration of Helsinki and followed the checklists for Strengthening the Reporting of Observational Studies in Epidemiology.14 Data were obtained from the prospectively designed Fight Retinal Blindness! RVO module of the Save Sight Registries.

All patients gave their informed consent.

Data sources and measurements This study reflected routine clinical care. Management decisions including choice and timing of
treatment were made at the discretion of the treating physician. The type of RVO (BRVO, HRVO or CRVO) was categorised by the treating physician at enrolment. A baseline visit captured demographic data when the first injection was administered. The number of letters read on a logarithm of the minimum angle of resolution VA chart (best of uncorrected, corrected or pinhole), central subfield thickness (CST in µm), the presence of cystoid macular oedema (CMO, active or inactive as judged by the treating physician), any treatments given, other procedures performed, and adverse events were recorded at baseline and follow-up visits.

Patient selection
We studied treatment-naïve patients with CMO due to HRVO commencing therapy with either aflibercept (2 mg Eylea, Bayer), bevacizumab (1.25 mg Avastin; Genentech, California, USA/Roche, Basel, Switzerland) or ranibizumab (0.5 mg Lucentis, Genentech/Novartis) between 1 January 2010 and 1 January 2020 in Australia, France, Ireland, Italy, the Netherlands, New Zealand, Spain and Slovakia—only centres auditing all three forms of RVO were included. This ensured comparison of HRVO with cohorts consisting entirely of BRVO and CRVO—free of any inadvertently included cases of HRVO. Eligible patients must have had at least three visits to establish sufficient ongoing follow-up.

Outcomes
The primary outcome was mean change in VA at 12 months. Secondary outcomes included mean change in CST, injections and visits, the proportion of eyes with VA >70 letters at 12 months, switching (at least two injections with an alternate VEGF agent or a single steroid agent) and non-completion (final visit <365 days). Outcomes were studied in all eyes with HRVO and compared separately to eyes with CRVO (vs HRVO) and BRVO (vs HRVO). We examined if undertreatment accounted for differences by further subgrouping based on the number of injections given.

Statistical analysis
Observations began at the first injection and continued until the 12 month visit (365±30 days). Baseline demographic characteristics with significant differences between HRVO versus BRVO and HRVO versus CRVO in bold (p<0.05).

| Table 1 | Demographic characteristics with significant differences between HRVO versus BRVO and HRVO versus CRVO in bold (p<0.05) |
|---------|---------------------------------------------------------------------------------------------------------------|

|          | HRVO | BRVO | P value vs HRVO | CRVO | P value vs HRVO |
|----------|------|------|----------------|------|----------------|
| Eyes, n  | 79   | 590  |                 | 344  |                |
| Patients, n | 78  | 580  |                 | 344  |                |
| Gender, % female | 48  | 51   | 0.75            | 41   | 0.31           |
| Age, mean years (SD) | 71 (11) | 70 (11) | 0.53          | 70 (12) | 0.68          |
| VA, mean letters (SD) | 53.8 (17.7) | 59.4 (14.9) | 0.009       | 51.9 (18.7) | 0.40       |
| VA >70 letters, % | 24   | 32   | 0.15            | 21   | 0.54           |
| VA ≤35 letters, % | 20   | 9    | 0.007           | 22   | 0.88           |
| CST, mean microns (SD) | 550 (186) | 482 (159) | 0.004        | 630 (223) | 0.002        |
| Initial treatment |       |       |                 |       |                |
| Bevacizumab | 33%  | 32%  | 0.90            | 26%  | 0.27           |
| Ranibizumab | 37%  | 39%  | 0.71            | 41%  | 0.52           |
| Aflibercept | 30%  | 29%  | 0.79            | 32%  | 0.79           |

P values reflect comparison of HRVO versus BRVO or comparison of HRVO versus CRVO.
BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CST, central subfield thickness; HRVO, hemiretinal vein occlusion; VA, visual acuity.
We applied the same subgrouping—HRVO eyes presenting with VA of controlling for them using ANCOVA. The adjusted VA changes baseline VA for each RVO subtype, we explored the effect of −0.45, p<0.001). Having acknowledged inherent difference in VA strongly correlated with larger changes in VA in all eyes (R

Visual outcomes at 6 and 12 months
VA in HRVO eyes started closer to the CRVO eyes but soon resembled that of the BRVO eyes once treatment began (table 1 and figure 1A). This led to large mean (CI) changes in VA in HRVO eyes at 6 and 12 months of +16.1 (12.6, 19.6) and +16.4 (13.1, 19.7) letters respectively, which were significantly greater than the corresponding changes in eyes with either BRVO (+10.4; p=0.003 and +11.4; p=0.006), or CRVO (+8.8; p<0.001 and +8.5; p<0.001).

Secondary visual outcomes were similar in HRVO and BRVO eyes. The proportion of HRVO eyes with final VA >70 letters was 68%—as it was in the BRVO controls. The CRVO eyes fared less well than HRVO eyes in most respects, including final VA >70 letters (45%; p<0.001), final VA ≤35 letters (16% vs 3%; p<0.001) and loss of ≥15 letters (13% vs 1%; p<0.001).

The SCORE2 study reported higher VA gains in eyes with CRVO eyes compared with BRVO eyes (550 µm vs 630 µm; p=0.002). The separation continued to 12 months (319 µm vs 371 µm; p=0.001). The mean change in CST was highest in the CRVO group (−259 µm) but it was not significantly greater than HRVO eyes (p=0.33). After controlling for baseline CST, the adjusted CST change in HRVO and BRVO were similar (p=0.42, table 2).

The mean CST at baseline was lower in HRVO eyes compared with CRVO eyes (550 µm vs 630 µm; p=0.002). The separation continued to 12 months (319 µm vs 371 µm; p=0.001). The mean change in CST was highest in the CRVO group (−259 µm) but it was not significantly greater than HRVO eyes (p=0.33). After controlling for baseline CST, the adjusted CST change was significantly greater in HRVO compared with CRVO (p=0.019, table 2).

Twelve (15%) of the HRVO eyes never had a single visit without active CMO during the study compared with 25% of CRVO eyes (p=0.07) and 29% of BRVO eyes (p=0.007).

Treatments and visits
The HRVO completers (89%) had medians (Q1, Q3) of 8 (6, 10) injections and 9 (9, 11) visits over 12 months with means of 4.9 injections given in the first 6 months and 2.5 injections in the final 6 months—none of which were significantly different to the eyes with BRVO or CRVO. Only two eyes with HRVO had focal laser treatment.

Eyes with HRVO consistently outperformed BRVO and CRVO irrespective of total injections given. We checked if the trend was due to undertreatment in our study by splitting completers in two groups based on injections received (figure 2). We used ≥7 injections (mean 9.4) to create one group that resembled treatment in pivotal RCTs and another group to represent possible undertreatment with <7 injections (mean 4.2).16–19 Eyes treated with ≥7 injections (65%) had mean change in VA with HRVO, BRVO and CRVO of +16.6, +13.6 and +10.8 letters, respectively. The remainder (35%) that received <7 injections had mean change in VA for HRVO, BRVO and CRVO of +12.5, +8.9 and +7.3 letters, respectively.

Switching and dropout
Switching VEGF inhibitors occurred in 11 HRVO eyes (14%) which was most commonly to aflibercept (six eyes) and from bevacizumab (five eyes) with very similar switching patterns in the control groups (figure 3). Only one HRVO eye switched to a steroid (dexamethasone implant) in 12 months. Steroid switching occurred in 6% of both the BRVO and CRVO groups when mean change in VA was +3 and −5 letters, respectively. The higher rate of steroid switching compared with HRVO was not statistically significant.

Eyes that did not complete 12 months with HRVO did so with good outcomes. Nine eyes (11%) with HRVO dropped out at a median (Q1, Q3) of 164 (91, 293) days (figure 3), with mean final VA of 80 (69, 84) letters, mean VA change from baseline of +25 (17, 41) letters and mean final CST of 275 µm (265, 281). Some eyes may have completed successful treatment. Documented reasons for lost to follow-up included one patient going to another doctor and two declining further treatment.

Macular thickness
The mean CST in HRVO eyes approached that of the BRVO controls very soon after treatment commenced (figure 1B). This was achieved with a significantly greater mean change in CST in HRVO eyes compared with BRVO controls at 6 months (−214 µm vs −141 µm; p=0.003) and at 12 months (−231 µm vs −151 µm; p=0.003). The HRVO and BRVO groups had very similar mean final CST (319 µm vs 330 µm; p=0.31). After controlling for baseline CST, the adjusted CST change in HRVO and BRVO were similar (p=0.42, table 2).

The mean CST at baseline was lower in HRVO eyes compared with CRVO eyes (+15.6 vs CRVO+13.2; p=0.19) but there was a larger difference between HRVO and CRVO (HRVO+15.6 vs CRVO+5.9; p<0.001).
Adverse events

Pigmentary macular changes affecting vision occurred during follow-up in 4 HRVO eyes with a decline in vision from a mean (SD) VA 58 (28) letters at 6 months to 49 (28) letters at 12 months and included one eye that received retinal laser for documented proliferative disease. Scatter retinal photocoagulation was delivered to a total of 23 HRVO eyes that had mean (95% CI) change in VA at 12 months of +15 (7, 23) letters and that received 8 (4, 8) injections which was typical of other eyes with HRVO in the cohort. There were no cases of endophthalmitis, traumatic cataract or retinal detachment following 585 injections.

DISCUSSION

This analysis using the FRB! observational database found that HRVO was a distinct clinical entity at baseline and in response to VEGF inhibitors compared with BRVO and CRVO. VA at baseline in HRVO eyes was worse than BRVO and closer to CRVO while macular thickness at baseline placed HRVO between BRVO and CRVO eyes to concur with previous reports. Once treatment was underway, the mean VA and CST in HRVO almost mirrored BRVO through 12 months.

The mean change in VA over 12 months, the primary outcome, was significantly higher in eyes with HRVO (+16.4 letters) than with BRVO (+11.4 letters; \( p=0.006 \)) and with CRVO (+8.5 letters; \( p<0.001 \)). Mean change in CST was significantly greater in eyes with HRVO (+8.5 letters; \( p<0.001 \)). Treatment burden was similar CRVO irrespective of how many injections were given over 12 months.

The results of our study can be interpreted differently from a clinical or research point of view. The adjusted outcomes offer clinical prognostic utility to individual patients, that is, a patient with a certain VA would likely do equally well if they had a BRVO or HRVO but would fair less well if they had a CRVO. The unadjusted outcomes of our study are more relevant to trials typically use the unadjusted mean change in VA as the primary outcome, which was significantly different for BRVO and CRVO eyes to concur with previous reports.

| Table 2 | Six-month and 12-month outcomes in eyes with HRVO, compared with eyes with BRVO or CRVO |
|---------|------------------------------------|---------------------------------|---------------------------------|----------|
| Eyes, n | HRVO | BRVO | P value (vs HRVO) | CRVO | P value (vs HRVO) |
| VA (letters) | | | | | |
| VA baseline, mean (SD) | 53.8 (17.7) | 59.4 (14.9) | 0.009 | 51.9 (18.7) | 0.40 |
| VA 6 months, mean (SD) | 69.9 (13.7) | 69.8 (14) | 0.96 | 60.7 (21.6) | <0.001 |
| VA 12 months, mean (SD) | 70.2 (15.3) | 70.8 (14) | 0.74 | 60.4 (23) | <0.001 |
| Change in VA (letters) | | | | | |
| ΔVA 6 months, mean (95% CI) | 16.1 (12.6 to 19.6) | 10.4 (9.3 to 11.5) | 0.003 | 8.8 (6.6 to 11.1) | <0.001 |
| ΔVA 12 months, mean (95% CI) | 16.4 (13.1 to 19.7) | 11.4 (10.2 to 12.6) | 0.012 | 8.5 (6.1 to 10.9) | <0.001 |
| Adjusted ΔVA 12 months, mean (95% CI) | 15.6 (11.9 to 19.3) | 13.2 (11.1 to 15.2) | 0.19 | 5.9 (3.6 to 8.3) | <0.001 |
| Gained ≥15 letters, % | 49 | 38 | 0.07 | 40 | 0.17 |
| Lost ≥15 letters, % | 1 | 3 | 0.50 | 13 | <0.001 |
| >70 letters, baseline/12 months, % | 24/68 | 32/68 | 0.15/1.0 | 21/45 | 0.54/0.001 |
| ≤35 letters, baseline/12 months, % | 20/3 | 9/3 | 0.007/1.0 | 22/16 | 0.88/0.001 |
| Central subfield thickness (μm) | | | | | |
| CST baseline, mean (SD) | 550 (186) | 482 (159) | 0.004 | 630 (223) | 0.002 |
| CST 6 months, mean (SD) | 332 (112) | 342 (115) | 0.45 | 402 (213) | <0.001 |
| CST 12 months, mean (SD) | 319 (124) | 330 (105) | 0.31 | 371 (181) | 0.001 |
| Change in CST (μm) | | | | | |
| ΔCST 6 months, mean (95% CI) | −214 (−257 to −172) | −141 (−154 to −127) | 0.003 | −229 (−258 to −200) | 0.60 |
| ΔCST 12 months, mean (95% CI) | −231 (−277 to −184) | −151 (−166 to −137) | 0.003 | −259 (−287 to −231) | 0.33 |
| Adjusted ΔCST 12 months, mean (95% CI) | −218 (−253 to −183) | −204 (−224 to −184) | 0.42 | −173 (−195 to −150) | 0.019 |
| Treatment and visits | | | | | |
| Injections, median (Q1, Q3)* | 8 (6, 10) | 8 (5, 9) | 1.0 | 8 (5, 10) | 1.0 |
| Visits, median (Q1, Q3)* | 9 (9, 11) | 10 (8, 12) | 0.38 | 11 (8, 13) | 0.12 |
| Suspension of treatment, n (%)† | 12 (15) | 96 (16) | 1.0 | 41 (12) | 0.45 |
| Never became inactive in 12 months, n (%) | 12 (15) | 174 (29) | 0.007 | 85 (25) | 0.07 |
| VEGF switchers, n (%) | 11 (14) | 81 (14) | 1.00 | 36 (10) | 0.43 |
| Steroid switchers, n (%) | 1 (1) | 38 (6) | 0.07 | 20 (6) | 0.15 |
| Non-completion of 12 months, n (%) | 9 (11) | 100 (17) | 0.26 | 58 (17) | 0.30 |

Significant differences between HRVO vs BRVO and HRVO vs CRVO are in bold (\( p<0.05 \)).

Adjusted, using analysis of covariance controlling for first treatment age and baseline VA or CST as fixed effects and nesting within patients (both eyes) or the same practice as random effects.

*Calculated only in completers receiving VEGF monotherapy throughout with Generalised Poisson models used to generate \( p \) values.

†Periods >180 days containing recorded visits and no treatment.

BRVO, branch RVO; CRVO, central retinal vein occlusion; CST, central subfield thickness; HRVO, hemiretinal vein occlusion; VA, visual acuity; VEGF, vascular endothelial growth factor.
each type of RVO. This highlights the risk of bias when HRVO is merged with BRVO or CRVO in trials.

Our results suggest that inclusion of HRVO in BRVO trails could inflate VA and CST outcomes. The BRAVO and VIBRANT studies make no mention of including HRVO in their abstracts, however, HRVO contributed 16%–17% of eyes to the ranibizumab treatment arms of the BRAVO study (+18.3 letters, −345 µm).7 The VIBRANT study also included eyes with HRVO without reporting the proportion (+17 letters, −280 µm).8 Caution should be exercised in comparing different studies especially if the contribution made by HRVO is not declared. The BRVO outcomes in the present study and in our previous study of real-world outcomes of ranibizumab vs aflibercept in BRVO (+11 letters, −150 to −170 µm) were less impressive than those pivotal RCTs.20 Such findings are not unusual for a real-world study, but it is possible that the inclusion of HRVO in the RCTs could have widened the margin. For the sake of comparison, the MARVEL study (+16 to +18 letters, −170 to −200 µm), a smaller RCT comparing bevacizumab and ranibizumab in eyes with BRVO excluded eyes with HRVO.21

In a CRVO cohort, the mean change in VA may increase by including HRVO while mean change in CST may decrease. A recent non-inferiority study included 31% of eyes with HRVO in a CRVO cohort comparing bevacizumab to ranibizumab.12 The 6-month visual gains were surprisingly high (+16 to +17 letters) while CST changes were modest (−330 to −400 µm) with monthly treatment. The pivotal CRUISE study which excluded HRVO had smaller VA changes (+13 to +15 letters) and larger changes in CST (−450 to −460 µm).22

Figure 2  Boxplot of change on VA at 12 months with (A) <7 injections (35% of completers) or with (B) 7–13 injections (65% of completers). The boxes (first to third quartiles) contain median (bold line) with whisker extension at 50% of the IQR. BRVO, branch RVO; CRVO, central RVO; HRVO, hemiretinal vein occlusion; VA, visual acuity.

Figure 3  Kaplan-Meier survival curves describing time to (A) switching from original VEGF inhibitor and (B) non-completion by RVO type. BRVO, branch RVO; CRVO, central RVO; HRVO, hemiretinal vein occlusion; VEGF, vascular endothelial growth factor.
Randomisation aims to minimise selection bias so that any difference in outcome between groups can be explained only by the treatment. There is potential for confounding when stratification based on HRVO is not done and disproportionate contributions are made by HRVO to study groups receiving different treatments. For example, randomisation distributed 24 HRVO eyes to the aflibercept group (13%) and 31 eyes to the bevacizumab group (17%) in the Study of COMparative Treatments for Retinal Vein Occlusion 2 (SCORE2) study.12 Another comparative study had 15% HRVO in a ranibizumab unobstructed second venous trunk which is haemodynamically 6 months despite starting with significantly worse vision. HRVO compared with BRVO overlooks the fact that HRVO shares with BRVO the opportunity for the congested venous circulation to decompress via the retinal capillaries that cross the median raphe to the unaffected retinal venous system and the potential for development of an optociliary shunt that may be the only bypass for an occluded central retinal vein. The pathology of HRVO involves occlusion at one of two separate venous trunks passing through the lamina cribrosa prior to uniting into a common central vein.13 This may allow development of a third collateral process in HRVO anterior to the lamina cribrosa to the unobstructed second venous trunk which is haemodynamically significant.14

Treatment-naïve HRVO eyes receiving VEGF inhibitors in routine clinical practice had very good visual and anatomic outcomes. Eyes with HRVO started with VA and CST closer to eyes with CRVO but ended with 12-month VA and CST equivalent to eyes with BRVO and in doing so significantly outperformed both BRVO and CRVO in mean change in VA over 12 months. We provide evidence specific to HRVO which suggests that it should not be considered equivalent to BRVO or CRVO at presentation or when comparing responses to treatment. There is a potential risk of bias when reporting the efficacy of treatments for BRVO and CRVO if a significant proportion of eyes have HRVO.

Author affiliations
1Clinical Ophthalmology and Eye Health, The University of Sydney Save Sight Institute, Sydney, New South Wales, Australia
2Department of Ophthalmology, Westmead Hospital, Sydney, New South Wales, Australia
3Marsden Eye Specialists Laser LASIK Eye Cataract Glaucoma Eyelid & Oculoplastic, Parramatta, New South Wales, Australia
4University of Western Australia, Lions Eye Institute, Nedlands, Western Australia, Australia
5Ophthalmology Department, Royal Free London NHS Foundation Trust, London, UK
6Eye Clinic, Department of Clinical Science, Luigi Sacco University Hospital, Milano, Italy
7Department of Ophthalmology, Isala, Zwolle, The Netherlands
8Ophthalmology, Centre Hospitalier Universitaire de Dijon, Dijon, France
9Department of Ophthalmology, Mater Private Hospital, Dublin, Ireland
10Department of Ophthalmology, University Hospital – Nemocnica sv. Michala, Bratislava, Slovakia
11Department of Ophthalmology, Institute Clinic of Ophthalmology, Hospital Clinic, Barcelona, Spain
12Department of Ophthalmology, University of Zurich, Zurich, Switzerland

Acknowledgements
Fight Retinal Blindness! Investigators: Auckland District Health Board, New Zealand (Dr D Squirrel); Australian Eye Specialists (Bacchus Marsh, Victoria) (Dr N Jaros); Australian Eye Specialists (Wyndham, Victoria) (Dr N Jaros); Blink, Australian Capital Territory (Dr R Barry); Centre Hospitalier Saint Brieuc, France (Dr T Guillaumie, Dr A Miri); CHU de Dijon, France (Dr P Gabriele); Centre Ophthalmologique Vincennes Vision, France (Dr S Tick); Canberra Hospital, Australian Capital Territory (Dr R Essex, Dr I Wells); Central Coast Eye Specialist, New South Wales (Dr S Young); Centro de Ojos de La Coruña, Spain (Dr P Carnota); Clinica Oftalmovista Valencia, Spain (Dr R Gallego-Pinazo); Dorset Consultant Center, Victoria (Dr H Steiner); Eye Associates, New South Wales (Dr G Gillies, Dr A Hunt); Eye Wide Bay, Queensland (Dr Z Louw); Fundació Privada Hospital Asil de Granollers, Spain (Dr L Sarrast); Gladisville Eye Specialists, New South Wales (Dr S Young); Gordon Eye Surgery, New South Wales (Dr S Fraser-Bell); Hospital Can Misses, Spain (Dr A Higueras); Hospital Clinic de Barcelona, Spain (Ms S Alforja Castiella, Dr M Figueras-Roca, Mr J Zarranza-Ventura); Hospital Punta de Europa, Spain (Dr F Lavid); Hospital San Juan de Dios del Aljarafe, Spain (Dr M Alvarez Gil, Dr P Catalán Muñoz, Dr M Tenas Sempere); Hospital Universitario La Paz, Spain (Dr M Asencio Duran); Hospital Universitario Miguel Servet, Spain (Dr P CALVO, Dr J Sanchez); Hospital Universitario Virgen del Rocio, Spain (Dr M Rodriguez Maqueda); Insight Eye Clinic, Western Australia (Dr G Funesi); Isala, Zwolle, Netherlands (Dr D Ponsioen); Lions Eye Institute, Western Australia (Professor I McAllister); Luigi Sacco Hospital – University of Milan, Italy (Dr A Invernizzi); Maison rouge Ophthalmologico-center, France (Dr L Castelnuovo, Dr G Miche, Dr B Wolff); Marsden Eye Specialists, New South Wales (Dr J Arnold, Dr H Cass); Mater Private Hospital, Ireland (Dr L O’Toole); Montpellier Eye Clinic, France (Professeur M Daniau); Nemocnica sv. Michala a.s., Slovakia (Dr P Kusenda); North Queensland Retina, Queensland (Dr D Reddie); Retina & Macula Specialists (Hurstville), New South Wales (Dr S Nothling); Retina & Macula Specialists (Miranda), New South Wales (Dr S Nothling); Retina Associates, New South Wales (Dr S Fraser-Bell); Southern Eye Specialists (NZ), New Zealand (Dr P Every); Sydney Eye Hospital, New South Wales (Dr S Fraser-Bell); Tamworth Eye Centre, New South Wales (Dr P Northcliffe); Unidad de Gestion Clinica de Oftalmologia, Hospital de Taganana, Spain (Dr G Garay-Aramburu); Villoria Clinic, Spain (Dr D Velazquez Villoria).

Contributors MCG and DB are the inventors of the software used to collect the data for this analysis, they initiated the collaborative project and revised the paper. HM implemented the trial in the UK and revised the paper. VN monitored data collection for the whole trial. ARH implemented the trial in Australia and drafted and revised the statistical analysis plan with VN and MCG. ARH cleaned and analysed the data. ARH drafted and revised the paper with VN and MCG. ARH is guarantor. TP, P-HG, AJ, LOT and PK implemented the trial and revised the paper in the Netherlands, France, Italy, Ireland and Slovakia respectively. SA, JIA and ILM revised the paper.

Funding This work was supported by a grant from the Royal Australian NZ College of Ophthalmologists Eye Foundation (2007-2009) and a grant from the National Health and Medical Research Council, Australia (NHMRC 2010-1012).

Competing interests JIA, ILM, HM, P-HG, LOT and MCG are members of advisory boards for Novartis and Bayer. JIA, HM and MCG are also members of advisory boards for Allergan. PHG is a member of advisory boards for Horus. ARH, MCG and JIA report personal fees and others from Novartis, others from Bayer, outside the submitted work. DB received a research grant from Novartis. MCG and DB are inventors of the software used to collect the data for this analysis.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was obtained in Australia and New Zealand, Ireland, Spain, Slovakia, Italy and France for eyes included in this study from the...
REFERENCES

1. Chopdar A. Dual trunk central retinal vein incidence in clinical practice. Arch Ophthalmol 1984;102:85–7.

2. Hayreh SS, Hayreh MS. Hemi-central retinal vein occlusion: pathogenesis, clinical features, and natural history. Arch Ophthalmol 1980;98:1600–9.

3. Chopdar A. Hemi-central retinal vein occlusion: pathogenesis, clinical features, natural history and incidence of dual trunk central retinal vein. Trans Ophthalmol Soc U K 1982;102 (pt 2):241–8.

4. Argon laser photocoagulation for macular edema in branch vein occlusion. The branch vein occlusion Study Group. Am J Ophthalmol 1984;98:271–82.

5. Scott IU, VanVeldhuisen PC, Eden NL, et al. Baseline characteristics and response to treatment of participants with hemicentral compared with branch retinal or central retinal vein occlusion in the standard care vs corticosteroid for retinal vein occlusion (SCORE) study: score study report 14. Arch Ophthalmol 2012;130:1517–24.

6. Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. JAMA 2017;317:2072–87.

7. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010;117:1102–12.

8. Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the Vibrant study. Ophthalmology 2015;122:538–44.

9. Shaichi Z, Mahroo QT, Bunce C, et al. Anti-Vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. Cochrane Database Syst Rev 2020;7:Cd009510.

10. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 OPTIMUS study. Ophthalmology 2012;119:1024–32.

11. Korobelnik J-F, Holz FG, Roeder J, et al. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology 2014;121:202–8.

12. Vader MJ, Schauwvlieghe A-SME, Verbraak FD, et al. Comparing the efficacy of bevacizumab and ranibizumab in patients with retinal vein occlusion: the bevacizumab to ranibizumab in retinal vein occlusions (BRVO) study, a randomized trial. Ophthalmology Retina 2020;4:576–87.

13. Karia N. Retinal vein occlusion: pathophysiology and treatment options. OPHTH 2010;4:809–16.

14. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.

15. R Core Team. The R project for statistical computing. Vienna, Austria: R foundation for statistical computing, 2021. https://www.R-project.org/

16. Brown DM, Campochiaro PA, Bhistsukil RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology 2011;118:594–602.

17. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. Am J Ophthalmol 2013;155:429–37.

18. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology 2011;118:2041–9.

19. Clark WL, Boyer DS, Heier JS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: 52-week results of the Vibrant study. Ophthalmology 2016;123:300–6.

20. Hunt AR, Nguyen V, Creuzot-Garcher CP, et al. Twelve-month outcomes of ranibizumab versus aflibercept for macular oedema in branch retinal vein occlusion: data from the FRB1 registry. Br J Ophthalmol 2021;123:bjophthalmol-2020-318491.

21. Narayan R, Stewart M, Das T, et al. Grid laser with modified pro re nata injection of bevacizumab and ranibizumab in macular edema due to branch retinal vein occlusion: MARVEL report no 2. OPHTH 2016;10:1023–9.

22. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010;117:1124–33.

23. Scott IU, VanVeldhuisen PC, Ip MS, et al. SCORE2 report 2: study design and baseline characteristics. Ophthalmology 2017;124:245–56.

24. Green WR, Chan CC, Hutchins GM, et al. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. Retina 1981;1:27–55.

25. McAllister IL, Barry C. Collateral formation in hemicentral retinal vein occlusion. Aust N Z J Ophthalmol 1991;19:339–41.