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

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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.

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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).[7–11] 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.[12] To support that choice the authors cited a review article which argued HRVO was a variant of CRVO, with similar pathogenesis and risk factors.[13]

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 data were summarised using the mean, SD, median, first and third quartiles (Q1, Q3) and percentages where appropriate. Comparison between cases and controls used t-tests, Wilcoxon rank-sum tests, χ^2 tests and Fisher's exact tests where appropriate. Crude visual and anatomic outcomes used the last observation carried forward for non-completers. Outcomes were adjusted for baseline differences using analysis of covariance (ANCOVA). Visits were censored after any steroid injection to examine outcomes while only on VEGF inhibitors.

Generalised additive mixed effects models were used to plot longitudinal changes in VA and CST for each type of RVO while only on VEGF inhibitors. We reported the number of injections and visits for completers but also used generalised Poisson mixed models to compare groups incorporating all eyes up to completion, non-completion, or receipt of an intravitreal steroid. Kaplan-Meier survival curves were generated for event-based outcomes.

Analysis was performed in R V.4.1.0 (cran.r-project.org) utilising the lme4 (1.1–27.1) and mgcv (V.1.8–35) packages for linear and generalised additive mixed effects models respectively.[15] The survival (3.2–11) package was used to generate the Kaplan-Meier estimates.[15] A $p<0.05$ was considered statistically significant.

RESULTS

A total of 79 eyes (78 patients) diagnosed with HRVO fulfilled the selection criteria and were included in the analysis. The control groups included 590 eyes (580 patients) with BRVO and 344 eyes (344 patients) with CRVO.

Demographic characteristics

Baseline demographic characteristics are presented in table 1. The mean (SD) baseline VA in HRVO eyes was 53.8 (17.7) letters which was significantly worse than the BRVO eyes (59.4 letters; p=0.009) and closer to the CRVO eyes (51.9 letters; p=0.40).

The mean (SD) baseline CST in HRVO was 550 (186) µm, significantly greater than that of the BRVO eyes (482 µm; p=0.004) and significantly less than that of the CRVO eyes (630 µm; p=0.002).

There were 20% of eyes with VA ≤35 letters in the HRVO group, similar to 22% in the CRVO controls (p=0.88) but different from 9% in the BRVO controls (p=0.004). The proportion of eyes starting treatment on each VEGF inhibitor was similar.

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.

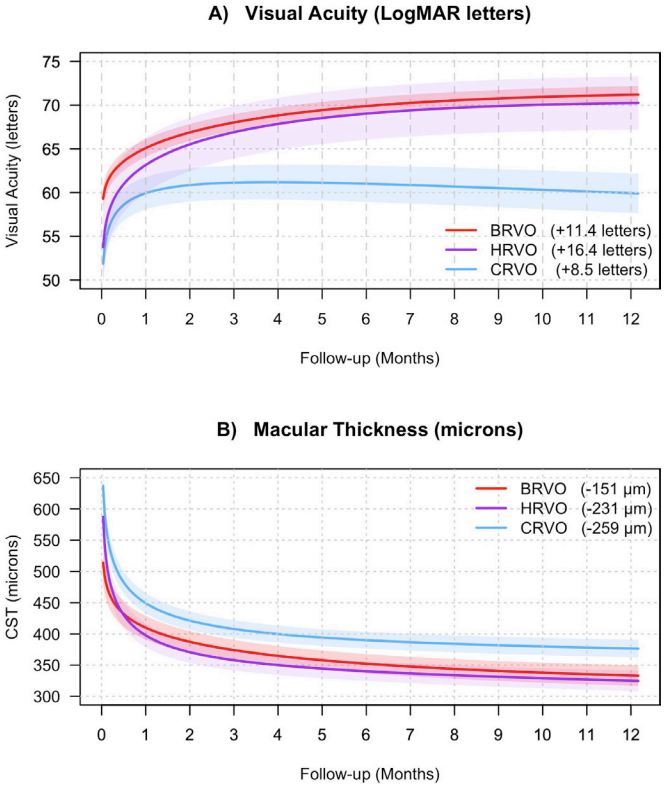

Figure 1 (A) Mean visual acuity and (B) Macular thickness over 12 months by RVO type. The HRVO group started with mean VA and CST more like the CRVO group but soon resembled the BRVO group. Shading indicates 95% CIs. The legend has the 12 months mean changes from baseline in VA and CST in parentheses. BRVO, branch RVO; CRVO, central RVO; CST, central subfield thickness; HRVO, hemiretinal vein occlusion; LogMAR, ogarithm of the minimum angle of resolution; VA, visual acuity.

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 lower baseline VA in HRVO eyes receiving VEGF inhibitors.[6] We applied the same subgrouping—HRVO eyes presenting with VA >58, 49–58 letters and 19–48 letters had median change in VA of +10, +23 and +28 letters, respectively. Lower baseline VA strongly correlated with larger changes in VA in all eyes (R −0.45, p<0.001). Having acknowledged inherent difference in baseline VA for each RVO subtype, we explored the effect of controlling for them using ANCOVA. The adjusted VA changes in BRVO were similar to HRVO (HRVO+15.6 vs BRVO+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).

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 (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.

Table 2 Six-month and 12-month outcomes in eyes with HRVO, compared with eyes with BRVO or CRVO

	HRVO	BRVO	P value (vs HRVO)	CRVO	P value (vs HRVO)
Eyes, n	79	590		344	
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)	**0.006**	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)					
Δ CST 6 months, mean (95% CI)	−214 (−257 to −172)	−141 (−154 to −127)	**0.003**	−229 (−258 to −200)	0.60
Δ CST 12 months, mean (95% CI)	−231 (−277 to −184)	−151 (−166 to −137)	**0.003**	−259 (−287 to −231)	0.33
Adjusted Δ CST 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.

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 (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 in HRVO eyes.

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.[5] 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 largest in CRVO, closely followed by HRVO which was significantly greater than BRVO eyes. Treatment burden was similar across all forms of RVO at around eight injections in this real-world study. HRVO eyes outperformed eyes with BRVO and 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 research. Trials typically use the unadjusted mean change in VA as the primary outcome, which was significantly different for

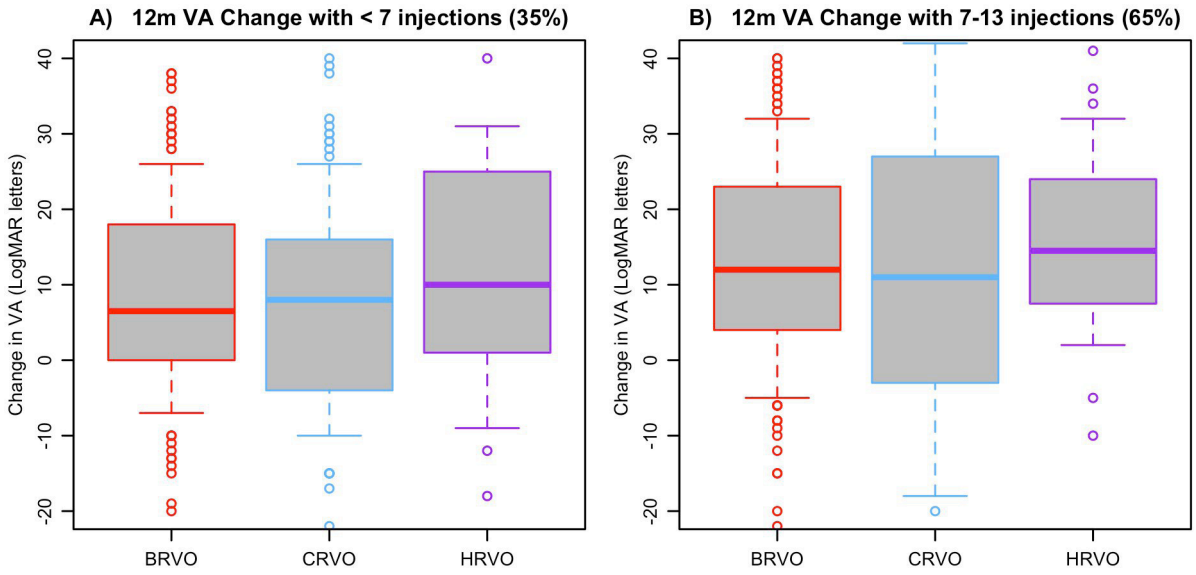

Figure 2 Boxplot of change on VA at 12 months with (A) <7 injections (35% of completers) or with (B) 7–13 injections (65% of completers). The boxes (first to third quartiles) contain median (bold line) with whisker extension at 50% of the IQR. BRVO, branch RVO; CRVO, central RVO; HRVO, hemiretinal vein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

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]

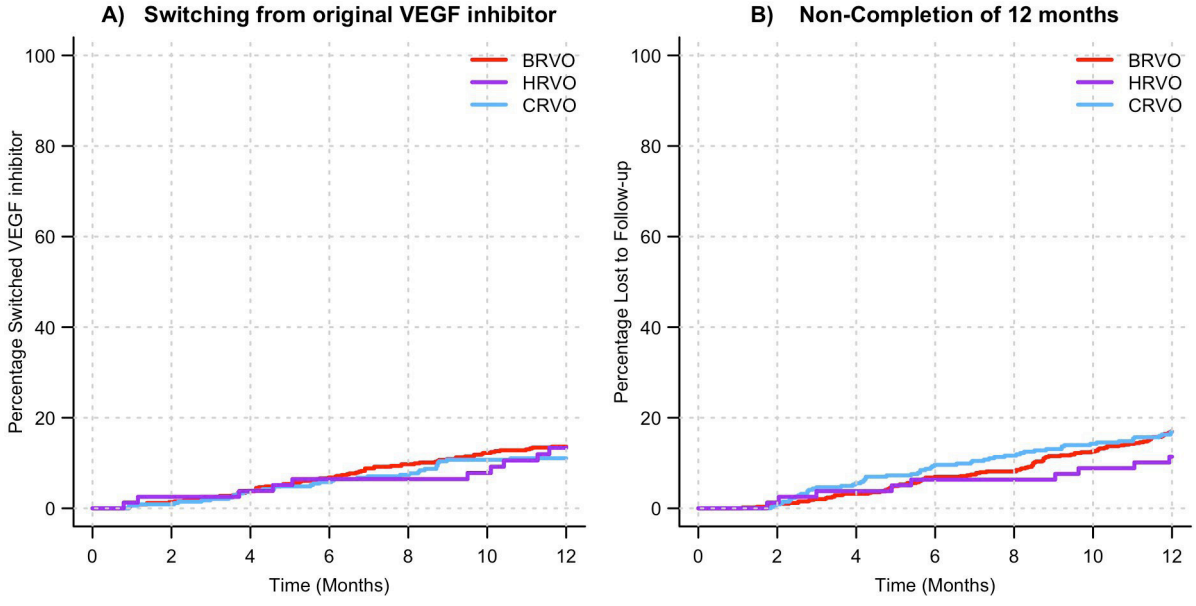

Figure 3 Kaplan-Meier survival curves describing time to (A) switching from original VEGF inhibitor and (B) non-completion by RVO type. BRVO, branch RVO; CRVO, central RVO; HRVO, hemiretinal vein occlusion; VEGF, vascular endothelial growth factor.

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.[23] Another comparative study had 15% HRVO in a ranibizumab group and 19% in a bevacizumab group when it compared outcomes in CRVO.[12]

There are some limitations inherent with the observational design of this study. The FRB! registry does not use reading centres and relies on the diagnosis and consistency of the treating physicians that are obliged to include least 85% of their relevant patients and finalise data entry in over 95% of visits to fulfil audit requirements. We are not aware of what drove treatment decisions, nor can we describe a protocol to reproduce these results. Switching VEGF agents (15%) probably reflected access to VEGF inhibitors over the duration of the study in keeping with normal clinical care. Steroid switching was more common in eyes with BRVO and CRVO compared with HRVO. We censored observations after steroid switching which may have selectively biased results by carrying forward the last observation when doing poorly on VEGF therapy. We wanted to study outcomes while on VEGF therapy only. The way in which we examined undertreatment as a possible cause for our findings was exploratory with subgrouping based on an outcome. It is possible that many eyes that received seven or more injections were undertreated and that many eyes were adequately treated with <7 injections.

The reason for the differences in outcomes in each type of RVO have not been explained by this study but may relate to a greater ability for eyes with HRVO to develop collateral vasculature as a means of improving venous outflow.[24] The lack of statistically significant difference in the adjusted outcomes for HRVO compared with BRVO overlooks the fact that HRVO caught up to match the mean final VA and CST of BRVO at 12 months despite starting with significantly worse vision. 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.[3] 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.[25]

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.

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