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Impact of retinal ischemia on functional and anatomical outcomes following anti-vascular endothelial growth factor therapy in patients with retinal vein occlusion

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Keywords

Vascular endothelial growth factor, VEGF, Anti-VEGF therapy; ischemic branch retinal vein occlusion; iBRVO; ischemic central retinal vein occlusion; iCRVO; ischemic retinal vein occlusion; iRVO; retinal ischemia; retinal vein occlusion; RVO; macular edema; retina; new vessels.

Summary statement

Eyes classified as having ischemic branch retinal vein occlusion (BRVO), based on the presence of ≥ 5 disc areas (DA) of retinal capillary non-perfusion (CNP) on fluorescein angiography (FFA), experienced higher visual acuity gain following anti-vascular endothelial growth factor (anti-VEGF) therapy than those with non-ischemic BRVO. The classification of ischemic versus non-ischemic RVO, based on the presence of ≥ 10 DA of retinal CNP, did not have an apparent detrimental effect on visual gain in eyes with CRVO.

Abstract

Purpose: To compare the impact of the classification of retinal vein occlusion (RVO) into ischemic or non-ischemic forms on outcomes following anti-vascular endothelial growth factor (anti-VEGF) therapy.

Methods: Retrospective review of consecutive patients with RVO evaluated at the Belfast Health and Social Care Trust between July 1st 2014 and December 31st 2015. Outcomes, including gain of ≥ 10 and ≥ 15 letters at 12 months, mean change in best-corrected visual acuity from baseline to 12 months, resolution of macular edema at 12 months and development of neovascular complications and epiretinal membrane following anti-VEGF therapy were compared between ischemic and non-ischemic eyes using regression models.

Results: One-hundred and seventeen eyes (115 patients), 58 with central (CRVO) and 59 with branch (BRVO) RVO, were included. A greater proportion of eyes with ischemic BRVO (iBRVO) gained ≥ 10 and ≥ 15 letters at 12 months than those with non-ischemic BRVO (niBRVO) ($p=0.005$ and $p=0.016$, respectively). No statistically significant differences in visual outcomes were observed between ischemic and non-ischemic CRVO. RVO classification was not associated with anatomical outcomes following treatment.

Conclusion: Findings support the use of anti-VEGFs in ischemic as well as non-ischemic forms of RVO.

Introduction

Retinal vein occlusion (RVO) is a relatively common retinal vascular disease that can lead to macular edema, ocular neovascularization, and visual loss¹⁻⁴. Presence and extent of retinal capillary non-perfusion (CNP) in RVO appears to confer a worse prognosis and a higher risk of complications⁵.

Intravitreal anti-vascular endothelial growth factor (VEGF) therapies have become the first line therapy for most patients with macular edema secondary to RVO⁶⁻¹². It has been shown that anti-VEGFs require frequent administration and long-term treatment for their effect to be maintained⁶⁻¹². Anti-VEGFs antagonize the effect of VEGF, which has been found to be increased in eyes with RVO¹³. VEGF appears to play a major role in RVO pathogenesis, including the development of macular edema and new vessel formation¹³.

Randomized clinical trials (RCTs) that investigated the clinical effectiveness of anti-VEGF therapy for the treatment of macular edema secondary to RVO, which form the evidence-based supporting their use in this retinal condition, did not include or included few patients with retinal ischemia at presentation¹⁴⁻¹⁹. Thus, the efficacy of anti-VEGFs in this group of patients remains uncertain. Many of these RCTs^{17,20-27}, however, investigated the development of retinal ischemia following anti-VEGF treatment, using the Central Retinal Vein Occlusion Study (CVOS)²⁸ and Branch Retinal Vein Occlusion (BRVO)²⁹ classification of ischemic CRVO (iCRVO) and ischemic BRVO (iBRVO). In this classification, ischemic RVO (iRVO) is defined by the presence and extension of retinal capillary non-perfusion (CNP) [≥ 10 disc areas (DA) for iCRVO and ≥ 5 DA for iBRVO].

This study aims at determining whether the classification of RVO based on the presence/extension of retinal capillary non-perfusion, as determined by the CVOS and BRVO, is associated with functional and/or anatomical outcomes following treatment with

anti-VEGFs. We also conducted a risk factor analysis to identify other factors that could have prognostic implications for anti-VEGF therapy response.

Patients and methods

The medical records of all patients with RVO presenting to ophthalmology clinics at the Belfast Health and Social Care Trust (BHSC), Belfast, Northern Ireland, United Kingdom, between July 1st 2014 and December 31st 2015 were reviewed. Patients were identified using an electronic database and, in addition, using surgical and laser lists/logbooks. Patients were considered eligible for the study if they had: 1) newly diagnosed RVO, 2) a fundus fluorescein angiogram (FFA) undertaken or had neovascularization at the time of presentation, 3) a minimum follow-up of 12 months and 4) received anti-VEGF therapy (i.e. ranibizumab, aflibercept or bevacizumab). Patients who did not meet these inclusion criteria, those who had other ocular diseases in addition to RVO which may affect vision (e.g. diabetic retinopathy, age-related macular degeneration) and those who received other treatments for macular edema secondary to RVO (i.e. steroids or macular laser) in addition to or instead of anti-VEGFs were excluded from the study. All consecutive patients that met these eligibility criteria were included. This study was part of an approved audit (audit number 5205) conducted at the BHSC; full ethical reviewed was waived.

Demographics , previous medical and ophthalmic history, best-corrected visual acuity (BCVA), central subfield retinal thickness (CST), persistence/resolution of macular edema, presence/absence of neovascular complications, presence/ absence of epiretinal membrane and number of anti-VEGF injections received during the 12 month period of follow-up were recorded. As this was a retrospective study, the treatment regimen and re-treatment decisions were at the discretion of the treating clinicians. The local protocol for treatment of RVO,

however, recommended during the study period three loading doses of monthly ranibizumab or aflibercept, followed by monthly review with further treatment based on a *pro re nata* (PRN) strategy (i.e. further injections undertaken if intraretinal or subretinal fluid was present).

Eyes with RVO were classified into ischemic or non-ischemic based on the area of retinal CNP observed on FFA images (Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany). As per the CVOS, iCRVO was defined by the presence of ≥ 10 disc areas (DA) of retinal CNP^{17,27,28}; iBRVO and ischemic hemicentral and hemispheric RVO (iHRVO) were defined by the presence of ≥ 5 DA of retinal CNP^{22-24,29}. For the purpose of this study, hemicentral and hemispheric RVO were grouped within BRVO. The status of the perifoveal capillary network (preserved, broken or unclassifiable) was also recorded. Eyes where FFA images were ungradable due to the presence of marked retinal hemorrhages or poor quality were considered 'unclassifiable'. Reading of all FFA images was conducted masked to functional and anatomical outcomes. Eyes with any ocular neovascularization detected at presentation were considered to have iRVO.

Best corrected visual acuity (BCVA) was measured prior to initiation of anti-VEGF treatment (at baseline) and at 12 months (± 3 months) using 4 meter ETDRS visual acuity charts with the patient's most current refraction; the ETDRS score obtained was used for the analysis.

Macular edema at baseline was defined by the presence of intraretinal or subretinal fluid at the macula and involving its center in the affected eye, as determined by spectral domain optical coherence tomography (SD-OCT) images (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Resolution of macular edema was defined by the

complete absence of intraretinal or subretinal fluid on SD-OCT at 12 months (± 3 months) following anti-VEGF treatment.

Presence of neovascularization in the iris (NVI), anterior chamber angle (NVA), optic disc (NVD) or elsewhere in the retina (NVE) as well as epiretinal membrane at baseline or developing anytime during the 12 months follow-up period were recorded for all eyes.

Data analysis

Data were entered into the statistical package for social sciences (SPSS Inc., Chicago, IL, USA, version 20.00), and a descriptive analysis was performed. Inferential models were fitted in the *R* software environment (*R* foundation for statistical computing, Vienna, Austria, version 3.4.3).

Associations between the classification (ischemic versus non-ischemic) and functional outcomes including the proportion of eyes gaining ≥ 10 and ≥ 15 ETDRS letters of visual acuity at 12 months and the mean change in vision from baseline to 12 months were estimated using log binomial models for dichotomous outcomes and multiple linear regression for continuous outcomes. Associations between the classification and anatomical outcomes, including the proportion of eyes with resolution of macular edema at 12 months, the mean change in CST and the proportion of eyes who developed neovascular complications and epiretinal membrane from baseline to 12 months were estimated using log binomial models and multiple linear regression analysis, as appropriate. Models were constructed including other factors that could potentially affect functional and anatomical outcomes including baseline vision; baseline CST; presence of primary open angle glaucoma (POAG), diabetes mellitus, hypertension and/or dyslipidemia; status of the perifoveal

capillary network (see above); presence of neovascular complications at presentation and number of injections received.

Given that only two patients had bilateral disease and contributed, thus, with both eyes to the study, no statistical corrections were made to account for the inclusion of both eyes of the same patient.

Results

A. Baseline characteristics

A total of 115 patients (117 eyes) met the inclusion criteria and were included in this study (Figure-1). There were 58 eyes with CRVO (iCRVO=17, niCRVO=41) and 59 with BRVO (iBRVO=17, niBRVO=42). Ischemic forms of both CRVO and BRVO presented with worse mean ($\pm$ SD) baseline vision [28 ± 22 ETDRS letters (6/75 Snellen equivalent) and 52 ± 20 ETDRS letters (6/24 Snellen equivalent), respectively) than non-ischemic forms [53 ± 18 ETDRS letters (6/30 Snellen equivalent) and 60 ± 14 ETDRS letters (6/18 Snellen equivalent), respectively]. Moreover, eyes with iCRVO and iBRVO had slightly greater CST at presentation than those with niCRVO and niBRVO (Table-1). Eyes with iRVO received slightly fewer anti-VEGF injections during the first year of treatment than those with non-ischemic forms. Baseline characteristics of included patients are summarized in Table-1.

B. Retinal ischemia, anatomical and functional outcomes following anti-VEGF therapy

Functional and anatomical outcomes in eyes with CRVO (iCRVO and niCRVO) and BRVO (iBRVO and niBRVO) at 12 months following anti-VEGF therapy are summarized in Table-2. Of the eyes included, 58% received ranibizumab only, 42% received aflibercept only, 5% started on ranibizumab and then switched to aflibercept and 2% received bevacizumab. A 10-

letter visual acuity gain was observed in a slightly greater proportion of eyes with BRVO than with CRVO. Similarly, the mean change in vision from baseline to 12 months was also greater in BRVO than in CRVO, with a mean visual acuity gain of 8 letters ($SD \pm 12$ letters) in BRVO when compared with 4 letters ($SD \pm 17$ letters) in CRVO. A greater number of eyes with iBRVO achieved visual acuity gains at 12 months following treatment than those with niBRVO (Table 2). In contrast, eyes with iCRVO had worse visual outcomes than niCRVO (Figure 2). Visual acuity of ≥ 69 ETDRS letters (Snellen equivalent of 6/12) at 12 months was achieved in 6%, 41%, 59% and 60% of eyes with iCRVO, niCRVO, iBRVO and niBRVO, respectively. Figure 3 shows an example of FFA image at baseline for a patient with iCRVO and SD-OCT images at baseline and at 12 months following anti-VEGF therapy.

The relative risk of eyes experiencing a visual acuity gain of ≥ 10 and ≥ 15 ETDRS letters in CRVO and BRVO at 12 months following anti-VEGF therapy, adjusted for other covariates studied, is presented in Table-3. Among BRVO patients, iBRVO was associated with two to three-fold increases in probability of improved visual acuity ($p=0.005$, $p=0.016$, for gains of ≥ 10 and ≥ 15 ETDRS letters respectively). This association was not found among patients with CRVO.

Worse baseline vision was associated with greater probability of gains of ≥ 10 letters at 12 months following treatment for both CRVO and BRVO. The greater the number of anti-VEGF injections, the greater the proportion of eyes experiencing ≥ 10 letter gain in CRVO ($p=0.005$). In contrast, in BRVO, eyes receiving a greater number of injections were less likely to gain ≥ 10 letters of vision ($p=0.005$).

Visual acuity changes from baseline to 12 months following anti-VEGF therapy in eyes with CRVO and BRVO adjusted for multiple covariates is presented in Table-4. There

was no significant difference between ischemic and non-ischemic eyes in terms of mean change in visual acuity from baseline to month 12 for either CRVO or BRVO ($p=0.749$ and 0.310 , respectively). Presence of POAG was associated with less improvement in visual acuity from baseline to 12 months in eyes with CRVO ($p=0.005$). Baseline CST was associated with changes in visual acuity in eyes with BRVO; eyes with greater CST at baseline had greater improvement in visual acuity at 12 months ($p=0.007$).

Relative risks of resolution of macular edema in eyes with CRVO and BRVO at 12 months following anti-VEGF therapy adjusted for multiple covariates are presented in Table-5. The classification of retina ischemia was not associated with resolution of macular edema at 12 months following anti-VEGF therapy in either CRVO or BRVO ($p=0.735$ and 0.958 , respectively). Absence of POAG was associated with halving of the risk of resolution of macular edema in eyes with CRVO ($p=0.010$). A greater number of anti-VEGF injections was negatively associated with resolution of macular edema in those with BRVO ($p=0.030$).

Changes in CST in eyes with CRVO and BRVO at 12 months following anti-VEGF therapy adjusted for multiple covariates are presented in Table-6. There was no association between the ischemic classification and changes in CST in either CRVO or BRVO eyes ($p=0.941$ and 0.113 , respectively). Absence of neovascularization was associated with a reduction in CST at 12 months following anti-VEGF therapy in eyes with BRVO ($p=0.046$).

The status of the perifoveal capillary network (as determined using FFA and as classified in the Methods section, above) was not associated with any of the functional or anatomical outcomes investigated, neither for eyes with CRVO nor for those with BRVO (Tables 3-6).

Due to the small number of eyes that developed neovascular complications and epiretinal membrane, inferential analysis based on these parameters was not possible.

Discussion

In this study, iCRVO (classified based on the presence of ≥ 10 DA of CNP) was not associated with a detrimental impact on functional outcomes, namely gain of ≥ 10 or ≥ 15 ETDRS letters of visual acuity at 12 months or on mean visual acuity change from baseline to 12 months, following anti-VEGF therapy after adjustment for other variables, including baseline BCVA. A greater proportion of eyes classified as having iBRVO (based on presence of ≥ 5 DA of CNP) had a visual gain of ≥ 10 and ≥ 15 ETDRS letters at 12 months, when compared with those with niBRVO after adjustment for other variables that could affect vision. The classification of iRVO was not associated with mean visual acuity change from baseline to 12 months or with anatomical outcomes, including resolution of macular edema at 12 months and mean change in CST following anti-VEGF therapy. These findings, based on evidence obtained from standard clinical practice, are important as they indicate that treatment of iRVO with anti-VEGFs does not appear to be less effective than treatment of niRVO, when the CVOS and BVOS classification is used to discern between ischemic and non-ischemic forms of the disease.

RCTs evaluating the clinical effectiveness of anti-VEGFs for the treatment of macular edema secondary to RVO included few or no patients with iRVO^{17,20-27}. Very few studies have evaluated the impact of the ischemic classification on outcomes following anti-VEGF in RVO. Two small observational retrospective cohort studies by DeCroos et al³⁰ (iCRVO=10; niCRVO=31) and Gokce et al³¹ (iCRVO=17, niCRVO=13), using the same definition of iCRVO than that used in the current study, did not find a statistically significant difference in mean gain of visual acuity or change in CST at 12 months following anti-VEGF therapy (bevacizumab) between iCRVO and niCRVO. A prospective study by Calugaru and

Calugaru³² which included 21 eyes with iCRVO and 36 eyes with niCRVO (using the CVOS definition) found no statistically significant difference between ischemic and non-ischemic cases in gain of ≥ 15 ETDRS letters ($\sim 45\%$ of eyes in both groups) at 36 months following anti-VEGF therapy (bevacizumab). However, statistically significant differences were observed in the mean change in visual acuity, with greater mean visual acuity improvement in eyes with iCRVO when compared with those with niCRVO. It is unclear, though, if corrections for baseline vision were undertaken. A small RCT²⁰ comparing ranibizumab (three monthly injections) with triamcinolone acetonide evaluated outcomes in eyes with iCRVO (n=17) versus those achieved in eyes with niCRVO (n=26) in the anti-VEGF treated arm. No statistically significant differences between the two groups in mean change in visual acuity or CST at 6 months were found (adjusted for baseline vision and CST).

COPERNICUS²⁶, an RCT that included 17 eyes with iCRVO and 98 eyes with niCRVO (using the CVOS definition) in the anti-VEGF (aflibercept) arm, showed a slightly lower proportion gaining ≥ 15 ETDRS letters at 12 months following treatment in eyes with iCRVO ($\sim 49\%$) when compared with those with niCRVO ($\sim 58\%$). Outcomes between groups were not formally compared so it is unclear whether this difference was statistically significant although it may be considered by some clinically relevant.

Similarly, only a few small studies have evaluated the impact of retinal ischaemia on outcomes following treatment with anti-VEGFs in eyes with BRVO. A small observational retrospective study by Cakmak et al³³ in which eyes were classified as iBRVO (n=7) or niBRVO (n=23) based on the BVOS definition (≥ 5 DA of retinal ischemia) found no statistically significant difference in mean change in vision between iBRVO and niBRVO at 6 months following anti-VEGF therapy (ranibizumab). There was also no statistically significant difference in changes in CST between groups. Two RCTs, VIBRANT³⁴ and that reported by Ramezani et al³⁵ found also no statistically significant difference between iBRVO

and niBRVO in mean change of visual acuity following anti-VEGF therapy. It should be noted that VIBRANT³⁴ defined iBRVO by the presence/ absence of ≥ 10 DA of retinal capillary non-perfusion. None of these studies, however, evaluated the association between the ischemic classification and the proportion of eyes improving ≥ 10 and ≥ 15 letters following anti-VEGF treatment.

The reason(s) why in the current study iBRVO conferred a better functional prognosis, after adjustment for other variables including baseline BCVA, than niBRVO following anti-VEGFs remains unclear. The type of occluded vessel (i.e. major versus macular) might have potentially played a role in the differential response observed as all eyes with iBRVO in the current series had the occlusion in a major branch, compared with only 48% of niBRVO eyes. A natural history study by Hayreh and Zimmerman comparing major BRVO (n=144) with macular BRVO (n=72) showed that eyes with major BRVO had better visual outcomes than those with macular BRVO at 15 months, correcting for presenting vision.² Although the proportion of eyes with a broken perifoveal capillary network was greater in eyes with niBRVO (69%) when compared with those with iBRVO (53%), this variable did not appear to have an impact on any of the functional variables investigated. ERM was present at the 12 months visit only in eyes with niBRVO; however, as ERM occurred in only a very small proportion (5%) of eyes, it is unlikely it would explain the differences in response observed between iBRVO and niBRVO.

In the current study, approximately a quarter of eyes with CRVO (26%) and BRVO (27%) gained ≥ 15 ETDRS letters of vision at 12 months following a mean of six and five anti-VEGF injections, respectively. A very similar result was observed in another retrospective clinic-based cohort study (CRVO=56; BRVO=100), in which a gain of ≥ 15 ETDRS letters at 12 months was achieved in 30% of eyes with CRVO and 24% of eyes with BRVO after a mean number of injections of 4 and 3, respectively³⁶. In contrast, previous

RCTs reported gains of ≥ 15 ETDRS letters at 12 months in greater proportions of affected eyes (45-60% of eyes with CRVO³⁷⁻⁴¹ and 57-65% of those with BRVO⁴¹⁻⁴⁴). This may be explained, at least partly, by the greater number of injections received in eyes enrolled in these RCTs (CRVO= 8-12; ^{26,37,38,40,41} BRVO= 6-9⁴¹⁻⁴⁴).

We investigated the impact of several variables on functional and anatomical outcomes following anti-VEGF therapy. Lower levels of vision at presentation were strongly associated with greater gain in vision following treatment for both CRVO and BRVO. Absence of POAG was associated with better visual outcomes and resolution of macular edema in eyes with CRVO. In those with BRVO, absence of hypertension and greater CST at baseline were associated with better visual outcomes. Few other studies have evaluated the role of presenting characteristics on outcomes following anti-VEGF therapy. Thus, a retrospective study by Sakanishi et al,⁴⁵ and two RCTs, CRYSTAL³⁵, and BRIGHTER⁴⁶ found that worse baseline visual acuity was strongly associated with better visual outcome (larger mean gain of vision) at 6,⁴⁶ 12^{35,45}, and 24^{47,48} months following anti-VEGF therapy for both CRVO and BRVO. Moreover, CRYSTAL and BRIGHTER reported that duration of CRVO and BRVO of less than three months was associated with better visual outcomes at 24 months following anti-VEGF therapy^{47,48}. A retrospective study by Mo et al,⁴⁹ which included 35 eyes with CRVO and 15 with BRVO, found the number of high reflective foci (HRF) in the outer retinal layer (ORL), as observed on SD-OCT, at baseline to be strongly associated with a poorer visual outcome at 12 months following anti-VEGF therapy in both CRVO and BRVO.

Strengths of this study include the thorough search strategy, using an electronic database and treatment logbooks, to identify eligible patients as well as the homogeneous definition of iRVO and of the follow-up of all patients included. Limitations include the retrospective study design and the fact that, although a relatively high number of RVO

patients were included, the number of each form of RVO (iBRVO, non-iBRVO, iCRVO and non-iCRVO) was relatively small. In addition, a higher number of patients in this cohort had the non-ischemic forms of CRVO and BRVO (70.89 and 71.19%, respectively) which may have had an impact on the findings presented herein.

Conclusion

In this study, the classification of iCRVO and iBRVO did not have an apparent detrimental effect on visual or anatomical outcomes following anti-VEGF therapy. Findings, thus, support the use of anti-VEGFs in ischemic and non-ischemic forms of RVO.

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Legends for Figures

Figure 1: Diagram presenting the process of identification of eligible patients for this study.

RVO: retinal vein occlusion; **FFA:** fundus fluorescein angiography; **NV:** neovascular complications; **anti-VEGF:** anti vascular endothelial growth factor; **DR:** diabetic retinopathy; **AMD:** age-related macular degeneration

Figure 2: Distribution of visual acuity changes at 12 months by type of retinal vein occlusion (RVO) [central (CRVO) /branch (BRVO)] and ischemic status, illustrating that the association between visual acuity change and ischemia differs between the two groups. For eyes with BRVO, visual acuity change was higher among ischemic eyes whereas the opposite was observed for eyes with CRVO.

Figure 3: Fundus fluorescein angiography (FFA) [left] and spectral-domain optical coherence tomography (SD-OCT) [right] of an 81 years old female patient with right ischemic central retinal vein occlusion (iCRVO). Baseline visual acuity was 9 ETDRS letters (6/192 Snellen equivalent). Following 6 anti-VEGF injections during the 12 months of follow-up visual acuity improved to 21 ETDRS letters (6/120 Snellen equivalent). Central subfield thickness (CST) was reduced from 793 μ m at baseline to 244 μ m at 12 months follow-up. Extensive areas of retinal capillary non-perfusion were observed on FFA (A); intraretinal fluid and disruption of retinal layers were detected on SD-OCT (B-1). At 12 months, resolution of intraretinal fluid and atrophy of retinal layers was detected on SD-OCT.

Table 1. Baseline characteristics of ischaemic and non-ischaemic retinal vein occlusion

	CRVO			BRVO		
	iCRVO	niCRVO	Total	iBRVO	niBRVO	Total
Number of eyes (n)	17	41	58	17	42	59
Age [years] Mean $\pm$ SD	73 $\pm$ 12	73 $\pm$ 11	73$\pm$17	72 $\pm$ 10	71 $\pm$ 12	71$\pm$12
Gender Male n (%)	8 (44%)	23 (56%)	31(53%)	9 (53%)	23 (55%)	32 (54%)
Eye involved Right n (%)	12 (67%)	22 (54%)	34 (59%)	8 (47%)	23 (55%)	31 (53%)
Systemic Disease n (%)						
Hypertension	13 (72%)	24 (59%)	37 (64%)	8 (47%)	28 (67%)	36 (61%)
DM	4 (22%)	11 (27%)	15 (26%)	3 (18%)	4 (10%)	7 (12%)
Dyslipidaemia	11 (61%)	26 (63%)	37 (64%)	6 (35%)	20 (48%)	26 (44%)
Ischaemic heart disease	2 (11%)	0	2 (3%)	1 (6%)	0	1 (2%)
Other cardiovascular dis.	7 (39%)	12 (29%)	19 (33%)	6 (35%)	10 (24%)	16 (27%)
Stroke	1 (6%)	1 (2%)	2 (3%)	1 (6%)	0	1 (2%)
Ophthalmic Diseases n (%)						
Glaucoma (POAG)	5 (28%)	7 (17%)	12 (21%)	0	13 (31%)	13 (22%)
History of RVO (different vein)	1 (6%)	3 (7%)	4 (7%)	1 (6%)	3 (7%)	4 (7%)
Vessel occluded n (%)						
Macular	N/A	N/A	N/A	0	22 (52%)	22 (37%)
Major	N/A	N/A	N/A	17 (100%)	20 (48%)	37 (63%)
Perifoveal capillary network at presentation n (%)						
Preserved	2 (11%)	23 (56%)	25 (43%)	7 (41%)	9 (21%)	16 (27%)
Broken	10 (56%)	15 (37%)	25 (43%)	9 (53%)	29 (69%)	38 (64%)
Unclassifiable	5 (29%)	3 (7%)	8 (14%)	1 (6%)	4 (10%)	5 (9%)
BCVA at presentation [ETDRS letters] <u>(Snellen equivalent)</u> Mean $\pm$ SD	28 $\pm$ 22 <u>(6/75)</u>	53 $\pm$ 18 <u>(6/24)</u>	46$\pm$22 <u>(6/36)</u>	52 $\pm$ 20 <u>(6/30)</u>	60 $\pm$ 14 <u>(6/18)</u>	58$\pm$16 <u>(6/21)</u>
BCVA [ETDRS letters (Snellen equivalent)] n (%)						
≥ 69 ($\geq 6/12$)	1 (6%)	16 (39%)	17 (29%)	9 (53%)	22 (52%)	31 (53%)
68-34 (6/18-6/60)	5 (29%)	18 (44%)	23 (39%)	6 (35%)	18 (43%)	24 (40%)
<34 (<6/60)	11 (65%)	7 (17%)	18 (31%)	2 (12%)	2 (5%)	4 (7%)
CST at presentation [μ m] Mean $\pm$ SD	662 $\pm$ 206	658 $\pm$ 176	659$\pm$183	519 $\pm$ 232	491 $\pm$ 140	499$\pm$170
NV at presentation n (%)	7 (39%)	0	7 (39%)	1 (6%)	0	1 (6%)
Iris NV	3	0	3	0	0	0
Angle NV	1	0	1	0	0	0
Disc NV	2	0	2	0	0	0
Elsewhere NV	1	0	1	1	0	1
Number of anti-VEGF injections Mean $\pm$ SD	5 $\pm$ 2	7 $\pm$ 2	6$\pm$3	5 $\pm$ 2	6 $\pm$ 2	5$\pm$2

***CRVO**: central retinal vein occlusion; **BRVO**: branch retinal vein occlusion; **i**: ischaemic; **ni**: non-ischaemic; **n**: number of eyes; **DM**: diabetes mellitus; **POAG**: primary open angle glaucoma; **BCVA**: best-corrected visual acuity; **CST**: central subfield thickness; **NV**: neovascular complications; **VEGF**: vascular endothelial growth factor; **N/A**: not

Table-2: Summary of functional and anatomical outcomes in eyes with CRVO and BRVO_at 12 months following anti-VEGF therapy

Outcomes	CRVO			BRVO		
	iCRVO (n=17)	niCRVO (n=41)	Total (n=58)	iBRVO (n=17)	niBRVO (n=42)	Total (n=59)
<u>Functional</u>						
Gain of ≥10 ETDRS letters n (%)	6 (35%)	16 (39%)	22 (38%)	12 (71%)	13 (31%)	25 (42%)
Gain of ≥15 ETDRS letters n (%)	3 (18%)	12 (29%)	15 (26%)	8 (47%)	8 (19%)	16 (27%)
Change of BCVA Mean± SD (ETDRS letters)	3±16	5±18	4±17	12±9	7±3	8±12
Final BCVA≥69 ETDRS letters (6/12 Snellen) <u>n (%)</u>	1 (6%)	17 (41%)	18 (31%)	10 (59%)	25 (60%)	(59%)
<u>Anatomical</u>						
Resolution of macular oedema n (%)	6 (35%)	16 (39%)	22 (38%)	16 (47%)	19 (46%)	35 (59%)
Change of CST Mean± SD (µm)	-222±260	-256±249	-246±250	-199±226	-128±173	-148±191
Development of NV complications n (%)	2 (12%)	2 (5%)	4 (7%)	2 (12%)	0	2 (3%)
Development of ERM n (%)	1 (6%)	1 (2%)	2 (3%)	0	2 (5%)	2 (3%)

***VEGF**: vascular endothelial growth factor; **n**: number of eyes; **BCVA**: best-corrected visual acuity; **ETDRS**: early treatment diabetic retinopathy study; **SD**: standard deviation; **CST**: central subfield thickness; **CRVO**: central retinal vein occlusion; **BRVO**: branch retinal vein occlusion; **i**: ischaemic; **ni**: non-ischaemic; **NV**: neovascular complication; **ERM**: epiretinal membrane.

Table-3: Relative risk of visual acuity gain of ≥ 15 and ≥ 10 ETDRS letters in eyes with CRVO and BRVO at 12 months following anti-VEGF therapy adjusting for multiple covariates

	CRVO						BRVO					
Covariates	Gain of ≥ 15 ETDRS letters			Gain of ≥ 10 ETDRS letters			Gain of ≥ 15 ETDRS letters			Gain of ≥ 10 ETDRS letters		
	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value
Ischemic status	0.53	(0.12, 2.45)	0.420	0.91	(0.39, 2.13)	0.835	3.57	(1.27, 10.03)	0.016	2.42	(1.31, 4.47)	0.005
Baseline CST	1.12	(0.62, 2.00)	0.714	1.17	(0.82, 1.67)	0.376	1.04	(0.76, 1.44)	0.792	1.00	(0.86, 1.15)	0.949
Absent POAG	0.93	(0.29, 2.96)	0.907	0.81	(0.41, 1.60)	0.549	0.67	(0.12, 3.89)	0.657	0.50	(0.23, 1.11)	0.089
Absent DM	1.47	(0.44, 4.89)	0.532	2.35	(0.83, 6.65)	0.108	4.28	(0.63, 29.05)	0.136	2.95	(1.10, 7.92)	0.032
Preserved perifoveal capillary network	1.39	(0.63, 3.05)	0.411	1.52	(0.78, 2.97)	0.223	0.52	(0.19, 1.45)	0.211	0.79	(0.54, 1.16)	0.236
Unclassifiable perifoveal capillary network	1.52	(0.55, 4.16)	0.416	1.43	(0.71, 2.88)	0.323	2.13	(0.51, 8.90)	0.299	1.32	(0.58, 2.98)	0.512
Number of anti-VEGF injections	1.45	(1.14, 1.84)	0.003	1.19	(1.05, 1.35)	0.005	0.83	(0.73, 0.96)	0.010	0.92	(0.87, 0.98)	0.005
Absent neovascular complications at presentation	1.12	(0.09, 13.82)	0.930	0.86	(0.21, 3.48)	0.834	2.51	(0.16, 39.91)	0.514	1.51	(0.34, 6.68)	0.588
Absent Hypertension	1.00	(0.82, 1.21)	0.970	1.40	(0.81, 2.44)	0.229	0.24	(0.08, 0.73)	0.012	0.49	(0.28, 0.85)	0.012
Absent dyslipidemia	1.20	(0.51, 2.84)	0.682	0.78	(0.43, 1.44)	0.433	2.14	(0.88, 5.19)	0.093	1.77	(1.02, 3.06)	0.041
Baseline BCVA	0.97	(0.94, 1.00)	0.086	0.98	(0.96, 1.00)	0.047	0.97	(0.94, 0.99)	0.020	0.97	(0.96, 0.99)	<0.001

* **CRVO:** central retinal vein occlusion; **BRVO:** branch retinal vein occlusion; **VEGF:** vascular endothelial growth factor; **n:** number of eyes; **BCVA:** best-corrected visual acuity; **ETDRS:** early treatment diabetic retinopathy study; **CST:** central subfield thickness; **DM:** diabetes mellitus; **POAG:** primary open angle glaucoma

Table-4: Visual acuity change in eyes with CRVO and BRVO at 12 months following anti-VEGF therapy adjusting for multiple covariates.

Covariates	CRVO				BRVO			
	estimate	Standard error	statistic	p-value	estimate	Standard error	statistic	p-value
(Intercept)	-24.81	13.68	-1.814	0.076	-5.83	11.33	-0.515	0.609
Ischemic status	2.03	6.31	0.322	0.749	3.71	3.61	1.027	0.310
Baseline CST	1.53	2.45	0.625	0.535	4.63	1.63	2.847	0.007
Absent POAG	16.29	5.51	2.959	0.005	0.61	3.82	0.160	0.873
Absent DM	8.68	5.64	1.538	0.131	2.01	5.18	0.388	0.700
Preserved perifoveal capillary network	-1.98	5.27	-0.376	0.709	-0.35	3.39	-0.104	0.917
Unclassifiable perifoveal capillary network	-0.38	7.55	-0.050	0.961	16.75	6.70	2.500	0.016
Number of anti-VEGF injections	1.02	1.05	0.970	0.337	-0.33	0.60	-0.550	0.585
Absent neovascular complications at presentation	2.21	9.74	0.227	0.821	12.95	11.99	1.080	0.286
Absent Hypertension	2.63	4.76	0.551	0.584	-3.85	3.13	-1.231	0.225
Absent dyslipidemia	1.46	5.01	0.292	0.772	5.27	2.90	1.816	0.076

***CRVO**: central retinal vein occlusion; **BRVO**: branch retinal vein occlusion; **VEGF**: vascular endothelial growth factor; **n**: number of eyes; **BCVA**: best-corrected visual acuity; **ETDRS**: early treatment diabetic retinopathy study; **CST**: central subfield thickness; **DM**: diabetes mellitus; **POAG**: primary open angle glaucoma

Table-5: Relative risk of resolution of macular oedema in eyes with CRVO and BRVO at 12 months following anti-VEGF therapy adjusting for multiple covariates

Covariates	CRVO			BRVO		
	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value
Ischemic status	0.86	(0.36, 2.06)	0.735	1.01	(0.82, 1.23)	0.958
Baseline CST	0.90	(0.62, 1.29)	0.554	0.90	(0.76, 1.07)	0.239
Absent POAG	0.49	(0.28, 0.84)	0.010	1.26	(0.68, 2.31)	0.466
Absent DM	2.03	(0.80, 5.15)	0.136	3.26	(0.62, 17.25)	0.165
Preserved perifoveal capillary network	1.09	(0.64, 1.88)	0.746	0.90	(0.64, 1.28)	0.571
Unclassifiable perifoveal capillary network	2.29	(0.86, 6.09)	0.097	0.75	(0.12, 4.77)	0.763
Number of anti-VEGF injections	1.01	(0.89, 1.15)	0.831	0.89	(0.80, 0.99)	0.030
Absent Hypertension	1.02	(0.51, 2.02)	0.958	1.49	(1.00, 2.22)	0.050
Absent dyslipidemia	0.66	(0.33, 1.33)	0.246	1.38	(0.82, 2.31)	0.221

***CRVO**: central retinal vein occlusion; **BRVO**: branch retinal vein occlusion; **VEGF**: vascular endothelial growth factor; **n**: number of eyes; **BCVA**: best-corrected visual acuity; **ETDRS**: early treatment diabetic retinopathy study; **CST**: central subfield thickness; **DM**: diabetes mellitus; **POAG**: primary open angle glaucoma

Table-6: CST change in eyes with CRVO and BRVO at 12 months following anti-VEGF therapy adjusting for multiple covariates.

Covariates	CRVO				BRVO			
	estimate	Standard error	statistic	p-value	estimate	Standard error	statistic	p-value
(Intercept)	77.11	202.40	0.381	0.705	216.88	188.48	1.151	0.255
Ischemic status	-6.97	93.92	-0.074	0.941	-103.71	64.20	-1.615	0.113
Absent POAG	-75.71	85.02	-0.890	0.378	10.25	68.75	0.149	0.882
Absent DM	-157.78	83.70	-1.885	0.065	4.63	92.96	0.050	0.960
Preserved perifoveal capillary network	16.39	80.45	0.204	0.839	43.70	60.37	0.724	0.472
Unclassifiable perifoveal capillary network	-74.15	117.31	-0.632	0.530	-137.14	119.96	-1.143	0.258
Number of anti-VEGF injections	-1.75	14.78	-0.118	0.906	7.90	10.87	0.727	0.471
Absent NV complications at presentation	-145.07	150.53	-0.964	0.340	-415.26	203.00	-2.046	0.046
Absent Hypertension	-13.22	72.86	-0.181	0.857	76.64	56.42	1.358	0.181
Absent dyslipidemia	19.36	74.67	0.259	0.797	-34.76	51.37	-0.677	0.502

***CRVO**: central retinal vein occlusion; **BRVO**: branch retinal vein occlusion; **VEGF**: vascular endothelial growth factor; **n**: number of eyes; **BCVA**: best-corrected visual acuity; **ETDRS**: early treatment diabetic retinopathy study; **CST**: central subfield thickness; **DM**: diabetes mellitus; **POAG**: primary open angle glaucoma; **NV**: neovascular complications.

Medical Record Screening and Identification of patients with newly
diagnosed RVO

1 July 2014 – 31 December 2015

Electronic records

Total retrieved
N=484

All RVO
N=473

New RVO
N=318

Not RVO
N=11

Not new incidence RVO
N=155

Log books

Total Retrieved
N=492

All RVO
N=41

New RVO
N=26

Not RVO
N=451

Not new incidence RVO
N=15

Total new RVO
N=344

With FFA/ NV
N=195

Follow-up ≥ 12 months
N=166

Anti-VEGF therapy
N=133

Only Anti-VEGF
therapy
N=124

Total included
N=117

No FFA or NV at presentation
N=149

Follow-up <12 months
N=29

No anti-VEGF therapy
N=33

Other therapies (steroids/ grid
macular laser)
N=9

Other retinal diseases (DR/
AMD)
N=7