Real-world Treatment Outcomes using Vascular Endothelial Growth Factor Inhibitors for Retinal Vein Occlusion

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STATEMENT OF ORIGINALITY

This is to certify that, to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any other purpose. I certify that the intellectual content is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Dr Adrian Hunt Date: 23rd February 2025

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ABSTRACT

Purpose: Describe and compare real-world outcomes using ranibizumab, aflibercept or bevacizumab for macular oedema due to branch, central or hemi-retinal vein occlusion (RVO).

Design: Retrospective, multicentre, international, observational study using data from the prospectively designed Fight Retinal Blindness! registry.

Methods: Longitudinal mixed effects models predicted adjusted visual acuity (VA) and central subfield thickness (CST) through 12 and 36 months.

Main outcomes measures: Mean change in VA (primary) and CST, injections, visits, completion, switching, suspensions of therapy and adverse events.

Results: Six analyses included a total of 2,918 treatment-naïve eyes that commenced VEGF inhibitors for RVO in routine care. Mean changes in VA were largest using aflibercept for CRVO or HRVO, overall ranging from +8 to +16 letters at 12 months after 7-8 injections, maintained at +10 letters with around 17 injections through 36 months. Aflibercept reduced CST sooner and by a greater amount than ranibizumab and bevacizumab in BRVO and CRVO. Non-completers had similar outcomes in BRVO but worse outcomes in CRVO than completers. Switching between different VEGF inhibitors was most frequently to aflibercept with similar outcomes but more injections. Eyes switched from a VEGF inhibitor to a steroid tended to have had no change or to have lost some VA compared with baseline. It could be inferred that around half of all eyes suspended treatment within 36 months of starting it. Adverse outcomes were in keeping with previous reports.

Conclusions: Real-world outcomes in RVO using VEGF inhibitors were good at 12 months considering fewer injections were given than in clinical trials and maintained through 36 months. Eyes with HRVO had the greatest 12-month gains in VA of all RVO types. We found aflibercept to be the most efficacious agent, followed by ranibizumab then bevacizumab, particularly in CRVO. Half of eyes with BRVO or CRVO still required injections at 36 months.

PUBLICATIONS INCLUDED IN THESIS

Niedzwiecki M, Hunt A✉, Nguyen V, Mehta H, Creuzot-Garcher C, Gabrielle PH, Guillemin M, Fraser-Bell S, Arnold J, McAllister IL, Gillies M, Barthelmes D. **12-month outcomes of ranibizumab versus aflibercept for macular oedema in central retinal vein occlusion: data from the FRB! registry.** Acta Ophthalmol. 2022 Jun;100(4). https://doi.org/10.1111/aos.15014

Hunt AR✉, Nguyen V, Creuzot-Garcher CP, Alforja S, Gabrielle PH, Zarranz-Ventura J, Guillemin M, Fraser-Bell S, Casaroli Marano RP, Arnold J, McAllister IL, O'Toole L, Gillies MC, Barthelmes D, Mehta H. **Twelve-month outcomes of ranibizumab versus aflibercept for macular oedema in branch retinal vein occlusion: data from the FRB! registry**. Br J Ophthalmol. 2022 Aug;106(8):1178-1184. https://doi.org/10.1136/bjophthalmol-2020-318491

Wang N, Hunt A, Nguyen V, Shah J, Fraser-Bell S, McAllister I, Barthelmes D, Gillies M, Squirrell D✉. **One-year real-world outcomes of bevacizumab for the treatment of macular oedema secondary to retinal vein occlusion**. Clin Exp Ophthalmol. 2022 Dec;50(9):1038-1046. https://doi.org/10.1111/ceo.14139

Hunt AR✉, Nguyen V, Arnold JJ, McAllister IL, Mehta H, Invernizzi A, Ponsioen T, Gabrielle PH, O'Toole L, Kusenda P, Alforja S, Barthelmes D, Gillies MC. **Hemiretinal vein occlusion 12-month outcomes are unique with vascular endothelial growth factor inhibitors: data from the Fight Retinal Blindness! Registry**. Br J Ophthalmol. 2023 Jun;107(6):842-848. https://doi.org/10.1136/bjophthalmol-2021-320482

Hunt A✉, Nguyen V, Bhandari S, Ponsioen T, McAllister IL, Arnold J, Young S, Gabrielle PH, Mehta H, O' Toole L, Alforja S, Zarranz-Ventura J, Barthelmes D, Gillies M. **Central Retinal Vein Occlusion 36-Month Outcomes with Anti-VEGF: The Fight Retinal Blindness! Registry.** Ophthalmol Retina. 2023 Apr;7(4):338-345. https://doi.org/10.1016/j.oret.2022.11.001

Alforja S / Hunt A (equal first), Nguyen V, O'Toole L, Gabrielle P-H, Invernizzi A, Mehta H, Ponsioen T, Squirrell D, Casaroli-Marano RP, Barthelmes D, Gillies M, Zarranz-Ventura J✉. **Three-year outcomes of vascular endothelial growth factor inhibitors in naïve branch retinal vein occlusion: Fight Retinal Blindness!** Ophthalmol Retina 2024 Apr 18:S2468-6530(24)00189-1. https://doi.org/10.1016/j.oret.2024.04.014

PRESENTATIONS

Hunt A, Gillies M & FRB! Investigators. **Outliers of Treatment Frequency in Retinal Vein Occlusion: 24-Month Comparative Analysis of Fight Retinal Blindness! Practitioners.**

Hunt A: Oral presentation to the European Society of Retinal Specialists Annual Meeting EURETINA Barcelona, Spain 18 – 22 September 2024

Hunt A: Oral presentation to the Annual Scientific Congress of the Royal Australian and New Zealand College of Ophthalmologists, Best Papers, Adelaide, Australia, Nov 1 - 4 2024. Awarded Australian Vision Research recommended abstract.

Hunt A, Gillies M & FRB! Investigators. **Attempted Cessation of VEGF inhibitors for RVO: data from the Fight Retinal Blindness! Registry.**

Hunt A: Oral presentation to the European Society of Retinal Specialists Annual Meeting EURETINA Amsterdam, Netherlands 5 – 8 October 2023

Hunt A, Nguyen V, Bhandari S, Ponsioen T, McAllister IL, Arnold J, Young S, Gabrielle PH, Mehta H, O' Toole L, Alforja S, Zarranz-Ventura J, Barthelmes D, Gillies M. **Central Retinal Vein Occlusion 36-Month Outcomes with Anti-VEGF: The Fight Retinal Blindness! Registry.**

Hunt A: Oral presentation to the European Society of Retinal Specialists Annual Meeting EURETINA Amsterdam, Netherlands 5 – 8 October 2023

Hunt A: Oral presentation to the Association for Research in Vision and Ophthalmology Annual Meeting ARVO 2022, 1-6 May in Denver, USA.

Hunt A: Oral presentation to the Annual Scientific Congress of the Royal Australian and New Zealand College of Ophthalmologists, Brisbane, Australia, Oct 28 - 1 Nov 2022. Awarded Australian Vision Research recommended abstract.

Hunt AR, Nguyen V, Arnold JJ, McAllister IL, Mehta H, Invernizzi A, Ponsioen T, Gabrielle PH, O'Toole L, Kusenda P, Alforja S, Barthelmes D, Gillies MC. **Hemiretinal vein occlusion 12-month outcomes are unique with vascular endothelial growth factor inhibitors: data from the Fight Retinal Blindness! Registry.**

Hunt A: Oral presentation to the European Society of Retinal Specialists Annual Meeting EURETINA Hamburg, Germany 2nd November 2022.

Hunt AR, Nguyen V, Creuzot-Garcher CP, Alforja S, Gabrielle PH, Zarranz-Ventura J, Guillemin M, Fraser-Bell S, Casaroli Marano RP, Arnold J, McAllister IL, O'Toole L, Gillies

MC, Barthelmes D, Mehta H. **Twelve-month outcomes of ranibizumab versus aflibercept for macular oedema in branch retinal vein occlusion: data from the FRB! registry.**

Hunt A: Oral presentation to the European Society of Retinal Specialists Annual Meeting EURETINA *Virtual* September 10th, 2021.

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LIST OF ABBREVIATIONS

Afl	Aflibercept
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
BCVA	Best-corrected visual acuity
Bvz	Bevacizumab
BRAVO	Ranibizuma*B* for the treatment of macular edema following B*RA*nch Retinal *V*ein *O*cclusion study
BRVO	Branch retinal vein occlusion
BVOS	Branch Vein Occlusion Study group
CI	Confidence interval
CMO	Cystoid macular oedema
CMT	Central macular thickness
CQR	Clinical Quality Registries
CRT	Central retinal thickness
CRUISE	Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study
CRVO	Central retinal vein occlusion
CSME	Clinically significant macular edema
CST	Central sub-field thickness
CVOS	Central Vein Occlusion Study group
CWS	Cotton wool spot
DMO	Diabetic macular oedema
DNA	Deoxyribonucleic acid
DR	Diabetic retinopathy
DRIL	Disorganisation of the retinal inner layers
EDTRS	Early Treatment of Diabetic Retinopathy Study
EMA	European Medicines Agency
EMR	Electronic Medical Record
ERG	Electroretinography
ERM	Epiretinal membrane
EZ	Ellipsoid zone
Fab	Fragment antigen-binding
FDA	U.S. Food and Drug Administration
FFA	Fundus fluorescein angiography
FRB!	Fight Retinal Blindness! registry
GAMMs	Poisson generalised additive mixed effects models
HF	Hyperreflective foci
HRVO	Hemicentral retinal vein occlusion
IL-8	Interleukin-8
IOP	Intraocular pressure
IRB	Institutional Review Board
IRF	Intra-retinal fluid
IRIS	Intelligent Research in Sight
IVTA	Intravitreal triamcinolone acetonide
KM	Kaplan-Meier
L-CRA	Laser Chorio-Retinal Anastomosis
LOCF	Last-observation-carried-forward

LOESS	Locally estimated scatterplot smoothing
Log MAR	Logarithm of minimal angle of resolution
MCP-1	Monocytochemotactic protein-1
MO	macular oedema
mRNA	Messenger ribonucleic acid
n	Number
nAMD	Neovascular age-related macular degeneration
NHS	National Health Service
NV	Neovascularisation
NVA	Neovascularisation of the angle
NVD	Neovascularisation at the disc
NVE	Neovascularisation elsewhere
NVG	Neovascular glaucoma
NVI	Neovascularisation of the iris
OCT	Optical coherence tomography
PDGF-AA	Platelet Derived Growth factor
PRN	*Pro-re-nata* (Latin: “for the thing born”)
PRP	Panretinal photocoagulation
Q1, Q3	First and third quartiles
RAPD	Relative afferent pupillary defect
Rbz	Ranabizumab
RCT	Randomised clinical trial
RETAIN	Macular edema due to b*R*anch r*ET*inal vein occlusion or centr*A*l retinal ve*I*n occlusio*N* study
RVO	Retinal vein occlusion
RWD	Real-world data
RWE	Real-world evidence
RWS	Real-world study
SCORE	Standard Care vs Corticosteroid for Retinal Vein Occlusion
SD	Standard deviation
SE	Standard error
SOC	Standard of care
SRF	Sub-retinal fluid
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TAE	treat and extend
TGA	Therapeutic Goods Administration
TNF-α	Tumour Necrosis Factor alpha
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VMT	Vitreomacular traction
Δ	Delta or Change

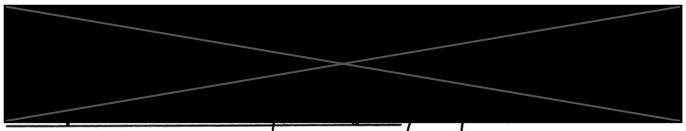
AUTHORSHIP ATTRIBUTION STATEMENTS

Chapter four is published as –

Niedzwiecki M, Hunt AR, Nguyen V, et al. 12-month outcomes of ranibizumab versus aflibercept for macular oedema in branch retinal vein occlusion: data from the FRB! registry. Acta Ophthalmol. 2022 Jun;100(4). https://doi.org/10.1111/aos.15014

STATEMENT FROM CANDIDATE

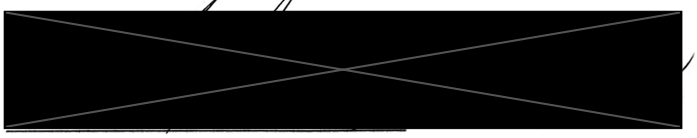
I designed the study, entered data, analysed the data, drafted the methods/results and revised the manuscript



Adrian Hunt

STATEMENT FROM THE SUPERVISOR

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statement above is correct.



Professor Mark Gillies

Chapter six is published as –

Wang N, Hunt A, Nguyen V, et al. One-year real-world outcomes of bevacizumab for the treatment of macular oedema secondary to retinal vein occlusion. Clin Experiment Ophthalmol. 2022;50(9):1038-1046. doi:10.1111/ceo.14139

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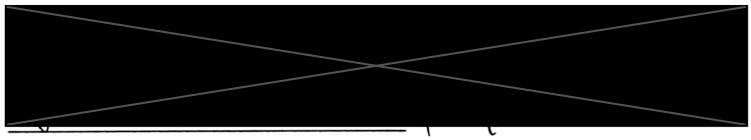

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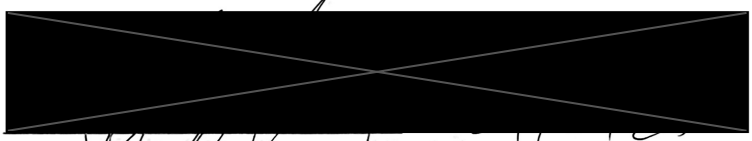

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Chapter nine is published as –

Alforja S / Hunt AR (equal), Nguyen V, et al. Three-Year Outcomes of VEGF Inhibitors in Naive Branch Retinal Vein Occlusion: Fight Retinal Blindness! Ophthalmol Retina. 2024 Oct;8(10):962-970.
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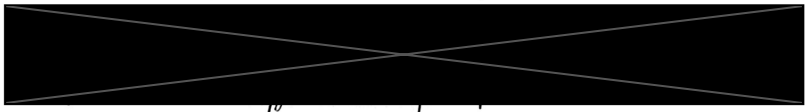

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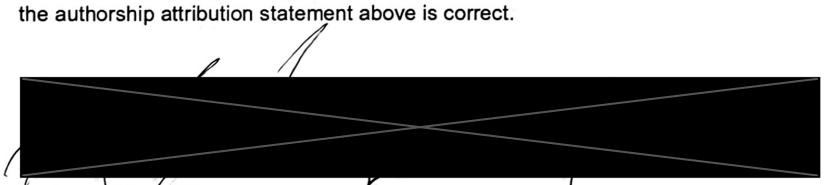


Professor Mark Gillies

CHAPTER 1: INTRODUCTION

1.1 Motivation and Aim of the Thesis

My involvement with the Fight Retinal Blindness! (FRB!) registry has informed my patients of their progress, informed me of the quality of care that I deliver and contributed to the larger FRB! project of international collaborative observational research regarding real-world outcomes of intravitreal therapy for retinal disease.

I have always had a strong interest in evidence-based medicine founded on my education as a graduate of the University of Sydney Medical School, as a Master of Biomedical Engineering and as a retinal subspecialist ophthalmologist. The postgraduate engineering degree is probably surprising, but it taught me different ways of thinking, seeing problems from a mathematical viewpoint. It is frequently said that everything is measurable in ophthalmology, particularly in retinal practice. When I undertook this doctorate, the observational research using data from the FRB! registry had likely improved outcomes for patients with neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DMO) however retinal vein occlusion (RVO) was least studied.

The primary motivation for this thesis was to help improve real-world evidence (RWE) regarding management of patients with RVO using vascular endothelial growth factor (VEGF) inhibitors in routine practice. This aligned with the aims of the FRB! project in monitoring and optimising outcomes of intravitreal therapy in retinal disease (Gillies et al., 2014). The efficient capture of trial-like data from the real-world setting within the FRB! registry when analysed retrospectively can produce quality observational research that ultimately improves our management of future patients.

RWE complements evidence derived from randomised clinical trials (RCTs) in that it is more generalisable to patients we actually manage in routine care. Clinical trials certainly inform decision making but need to be interpreted with the understanding that they are like an

experiment, typically aimed at demonstrating the safety and efficacy of new treatments against existing standard of care. Well-resourced trials deliver protocol defined treatment to a highly select group of patients, but in routine practice we treat a broader range of patients that are less well supported to sustain the high burden of frequent treatment that was delivered in trials.

My candidature began visiting retinal practices, boosting data acquisition and enthusiasm in the RVO module. These visits were a privilege, giving me invaluable insights into the diversity of approaches taken by different doctors to the management of retinal vein occlusion in routine practice. I was fortunate that the FRB! community of practitioners embraced participation in the RVO module in Australia, New Zealand and European centres.

The next stage in the project involved development of my programming and statistical skills that enabled my completion of four 12-month analyses. As my candidature progressed the availability of longer-term data enabled my analysis of patient treatment outcomes for up to 36 months after commencing VEGF inhibitors for treatment-naïve CRVO and for BRVO in routine care.

The FRB! project is a large collaborative network involving around 100 doctors in over 20 countries. All analyses included in this thesis were performed by me using international FRB! data after implementing each study in Australia, drafting and revising each statistical analysis plan, cleaning and analysing the data and drafting and revising the methods and results sections of all manuscripts. In four first-authored manuscripts, I drafted and revised the entire manuscript. In two analyses, where senior authors were in Switzerland or New Zealand, I provided the completed methods and results sections, was assigned second authorship and revised the introduction and discussion sections first drafted by local fellows.

1.2 Organisation of the thesis

Structured research began at the early stages of candidature meaning much of this thesis consists of published works. It is organised in the traditional format of introduction, methods, results and conclusions. The results chapters consist of submitted manuscripts, however minor modifications have been made to improve coherence of the thesis, the referencing system has been unified to APA 6th (sections) and the published articles have been included in the appendix.

Chapter Two

This chapter reviews the epidemiology, pathophysiology, clinical features, diagnostic tests, natural history and management of RVO and the pivotal trial evidence supporting available treatments for RVO. The real-world evidence (RWE) is then reviewed along with a discussion of the complementary role that RWE has to RCT evidence. Registries are discussed including the value of using registry data to produce high-quality observational research. Knowledge gaps are identified that help formulate aims of the thesis.

Chapter Three

This chapter describes in more depth the overall methods of the thesis otherwise briefly covered in each manuscript. It includes a detailed description of the FRB! RVO module including all the data fields. A rationale is also provided for specific statistical methodologies employed in the analysis of large real-world datasets.

Chapter Four

The 12-month treatment outcomes were compared after commencing aflibercept or ranibizumab for macular oedema secondary to treatment-naïve central retinal vein occlusion (CRVO). The findings of this analysis, as it was accepted by the journal “Acta Ophthalmologica”, are presented in this chapter.

Chapter Five

The 12-month treatment outcomes were compared after commencing aflibercept or ranibizumab for macular oedema secondary to treatment-naïve branch retinal vein occlusion (BRVO). The findings of this analysis, as it was accepted by the “British Journal of Ophthalmology”, are presented in this chapter.

Chapter Six

The 12-month treatment outcomes were analysed after commencing bevacizumab in treatment-naïve eyes with RVO. The findings of this analysis, as it was accepted by the journal “Clinical and Experimental Ophthalmology”, are presented in this chapter.

Chapter Seven

The unique characteristics of treatment-naïve hemiretinal vein occlusion (HRVO) and the 12-month outcomes of treatment of HRVO with VEGF inhibitors were compared with BRVO and CRVO variants in routine clinical care. The findings of this analysis, as it was accepted by the “British Journal of Ophthalmology”, are presented in this chapter.

Chapter Eight

The 3-year outcomes were analysed in eyes with treatment-naïve CRVO after starting VEGF inhibitors in routine clinical practice. The findings of this analysis, as it was accepted by the journal “Ophthalmology Retina”, are presented in this chapter.

Chapter Nine

The 3-year outcomes were analysed in eyes with treatment-naïve BRVO after starting VEGF inhibitors in routine clinical practice. The findings of this analysis, as it was accepted by the journal “Ophthalmology Retina”, are presented in this chapter.

Chapter Ten

This chapter summarises the entire thesis, discusses key findings, acknowledges limitations of the research and draws conclusions. The chapter also provides discussion of areas needing further research.

Appendix

Visual acuity conversion chart for Logarithm of Minimum Angle of Resolution (LogMAR), patient information and consent form, conference materials (abstracts) and accepted publications are included. Other related papers not included in the thesis that were accepted for publication during the research period are also included.

1.3 References

Gillies, M. C., Walton, R., Liong, J., Arnold, J. J., McAllister, I., Morlet, N., . . . Barthelmes, D. (2014). Efficient capture of high-quality data on outcomes of treatment for macular diseases: the fight retinal blindness! Project. *Retina, 34*(1), 188-195. doi:10.1097/IAE.0b013e318296b271

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

This chapter introduces retinal vein occlusion (RVO), with particular emphasis on available treatments supported by phase III randomised clinical trials (RCTs). It reviews existing real-world evidence (RWE) regarding outcomes using vascular endothelial growth factor (VEGF) inhibitors in the management of RVO. It discusses the strengths and weaknesses of both the trial and real-world evidence. It then identifies knowledge gaps in need of further research. Finally, it explores the role of RWE in complementing trial evidence, particularly when it is derived from high-quality registry data, as a method of addressing these knowledge gaps.

2.1 Introduction to Retinal vein occlusion

Retinal vein occlusion is a common retinal vascular disease characterised by venous dilatation, retinal haemorrhages and oedema in the distribution of retina drained by the obstructed vein. Three variants exist based on the location of the occlusion including branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) and hemiretinal vein occlusion (HRVO). RVO commonly presents with acute unilateral painless loss of vision due to macular oedema in patients aged over 60 years with hypertension or atherosclerosis (Mitchell, Smith, & Chang, 1996; S. Rogers et al., 2010). RVO is the second most common sight-threatening retinal vasculopathy after diabetic retinopathy (Cugati, Wang, Rochtchina, & Mitchell, 2006). RVO causes significant morbidity, consumes considerable health resources and decreases vision-related quality of life (Awdeh et al., 2010; Deramo, Cox, Syed, Lee, & Fekrat, 2003; Fekrat et al., 2010). Current recommended treatment for RVO involves frequent intravitreal injections of VEGF inhibitors that are highly effective yet place significant burden on patients and carers.

2.1.1 Epidemiology

Population based studies have estimated that 16.4 million people worldwide were affected in 2010, including 2.5 million with CRVO and 13.9 million with BRVO (McIntosh et al., 2010; S.

L. Rogers et al., 2010). The Beaver Dam Eye Study estimated a cumulative incidence of 0.3%-0.5% for CRVO and 1.6%-2.7% for BRVO in an elderly population over a 9–15-year period (Klein, Moss, Meuer, & Klein, 2008). The estimated a prevalence of BRVO was 4.4 per 1000 people and 0.8 per 1000 people for CRVO after pooling large population studies in the United States, Europe, Asia and Australia (Arakawa et al., 2011; S. Rogers et al., 2010; Zhou et al., 2013). The Eye Disease Case-Control Study (EDCCS, 1993, 1996) identified risk factors for RVO including increased age, hypertension and glaucoma with additional risks for BRVO of smoking and for CRVO of diabetes and hyperlipidaemia. The predominantly systemic associations likely explain why 7% of patients with CRVO subsequently develop contralateral CRVO within 5 years (Hayreh, Zimmerman, & Podhajsky, 1994) and why 9%-10% of patients with BRVO have contralateral BRVO at presentation or subsequently develop it in the contralateral eye (BVOS_group, 1984, 1986).

2.1.2 Pathophysiology

Theories of aetiology in RVO are common to venous thrombosis in general. Virchow was credited with the aetiological triad of hypercoagulability, stasis and venous intimal injury in venous thrombosis (Dickson, 2004). Mechanical compression dominates any discussion of pathogenesis in BRVO (Kumar et al., 1998). The occlusion site in the vast majority (99%) of BRVOs is at a point of arteriovenous crossing where the adventitial lining is shared with the thickened wall of a retinal arteriole (Frangieh, Green, Barraquer-Somers, & Finkelstein, 1982; J. Zhao, Sastry, Sperduto, Chew, & Remaley, 1993). In CRVO, histopathological examination reveals thrombosis within or posterior to the lamina cribrosa, possibly due to an adjoining atherosclerotic central retinal artery causing impingement, turbulence or endothelial damage (Green, Chan, Hutchins, & Terry, 1981). As the third component of the triad, hypercoagulability associated with systemic haematological or inflammatory diseases should be considered when the presentation of RVO is bilateral or in a patient younger than 60 years of age (Fong & Schatz, 1993; Lahey et al., 2002).

It would be simplistic to consider the pathology of RVO merely an issue of plumbing as multiple angiogenic and inflammatory cytokines are also involved that further breakdown the blood retinal barrier and elevate interstitial fluid to compromise the already compromised retina (Derevjanik et al., 2002; Ozaki et al., 1997; Ozaki et al., 1999). Chief amongst these is Vascular Endothelial Growth Factor (VEFG), though others such as interleukin-8 (IL-8), monocytochemotactic protein-1 (MCP-1), Platelet Derived Growth factor (PDGF-AA) and Tumour Necrosis Factor alpha (TNF-α) also contribute to the pathology (Aiello et al., 1994; Campochiaro et al., 2008; Derevjanik et al., 2002; Jung, Kim, Sohn, & Yang, 2014; Kaneda et al., 2011; W. J. Lee, Kang, Seong, & Cho, 2012; Noma, Funatsu, Mimura, Harino, & Hori, 2009; Ozaki et al., 1997; Ozaki et al., 1999).

The therapeutic appeal of using newly developed VEGF inhibitors for RVO was heightened by the discovery of increased VEGF messenger ribonucleic acid (mRNA) transcription and intraocular levels of VEGF in RVO (Noma et al., 2005; Pe'er et al., 1998). The contribution of VEGF in the pathology of RVO is no better demonstrated than by the outstanding outcomes reported in pivotal trials which made VEGF inhibitors recommended first line therapy. (Boyer et al., 2012; Brown et al., 2011; Brown et al., 2013; Campochiaro et al., 2011; Campochiaro et al., 2015; Campochiaro et al., 2010; Clark et al., 2016; Derevjanik et al., 2002; Korobelnik et al., 2014; Ozaki et al., 1997; Ozaki et al., 1999; Shalchi, Mahroo, Bunce, & Mitry, 2020).

2.1.3 Clinical Features and Subtypes

Retinal haemorrhages are a sign common to all forms of RVO, distributed in the area of the retina normally drained by the affected vein. CRVO affects the entire retina, BRVO affects a wedge or quadrant of the retina, while HRVO affects the superior or inferior retina owing to an anatomical variation at the optic disc (Chopdar, 1982). The venous network distal to the occlusion is usually tortuous and dilated. In more severe occlusions the retina can be ischaemic with dense haemorhages, cotton wool spots (CWS) and in the case of an

ischaemic CRVO an afferent pupillary defect may be present. Though typically presenting because of macula oedema, a delayed presentation can also occur due to neovascular sequelae in the posterior segment causing vitreous haemorrhage or in the anterior segment causing neovascular glaucoma. (Sophie L. Rogers et al., 2010).

2.1.4 Diagnostics

Multi-modal imaging has become the norm in modern ophthalmology, particularly within retinal practices. Though the diagnosis of RVO is usually made through examination, imaging techniques employed in RVO include colour retinal photography, fundus fluorescein angiography (FFA), optical coherence tomography (OCT) and more recently OCT angiography (OCT-A).

FFA has historically been very important in RVO, particularly when laser photocoagulation was the primary treatment, by revealing vascular leakage and areas of ischaemia. However, the invention and widespread clinical adoption of OCT has made it the main tool for diagnosis and monitoring macular structure and anatomical response to treatment in RVO in the era of intravitreal therapy.

The OCT non-invasively provides near histological resolution images of the macula in cross section. The detection of macular oedema prior to OCT was only through slit-lamp examination using handheld lenses looking at the macula front-on. OCT provides a cross-sectional view adding both quantitative and qualitative information. Quantitative parameters most often used in clinical trials to assess anatomical outcomes include the central sub-field thickness (CST), or sometimes central macular or retinal thickness (CMT or CRT), which allows numeric comparison between visits and as a continuous variable lends itself to statistical analysis.

Qualitative OCT parameters can be particularly helpful in the clinical management of RVO, revealing the location of oedema (intra-retinal fluid [IRF], subretinal fluid [SRF]), hyperreflective foci (HF), disorganisation of the retinal inner layers (DRIL) and other degenerative changes in the macula (atrophy or thinning, pigmentary changes, disruption of the photoreceptor inner-outer segment layer or ellipsoid zone [EZ]) as well as vitreomacular interface abnormalities such as epiretinal membrane (ERM) or vitreomacular traction (VMT) (I. P. Chatziralli, Sergentanis, & Sivaprasad, 2016; Eldeeb, Chan, Sun, & Chen, 2018; Ko, Kwon, & Byeon, 2014; Tang et al., 2020).

OCT angiography (OCT-A) has emerged as a clinical imaging tool available in newer OCT machines, non-invasively identifying many of the vascular features of RVO previously only seen with FFA (Kashani, Lee, Moshfeghi, Durbin, & Puliafito, 2015). OCT angiography is starting to gain traction in RVO research. Though not the topic of this thesis, it can aid in the assessment of microvascular pathological changes in the macula in the deep and superficial retinal plexuses, in the choriocapillaris and collateral circulation (Casselholmde Salles, Kvanta, Amren, & Epstein, 2016; Ghashut et al., 2018; Hasegawa, Murakawa, Maruko, Kogure-Katakura, & Iida, 2019; Hasegawa, Takahashi, Maruko, Kogure, & Iida, 2019; Kang, Yoo, Jo, & Kim, 2017; Wakabayashi et al., 2017; Q. Wang et al., 2018; Winegarner et al., 2018).

Below are examples of a normal eye, CRVO, BRVO and HRVO. Figures 2.1 to 2.5 include fundus photographs, OCT scans and thickness maps, examples of fluorescein angiography and, given the topic of the thesis, examples of the impressive anatomical response to intravitreal therapy using VEGF inhibitors (Scans and Photos: PhD candidate).

Figure 2.1. The posterior segment of a normal left eye with visual acuity (VA) of 6/6 (85 log MAR [Logarithm of minimal angle of resolution] letters). A) Colour fundus photograph showing the normal optic disc, retinal vasculature and macula. B) OCT raster through the central macula. C) OCT thickness map with CST of 226 microns.

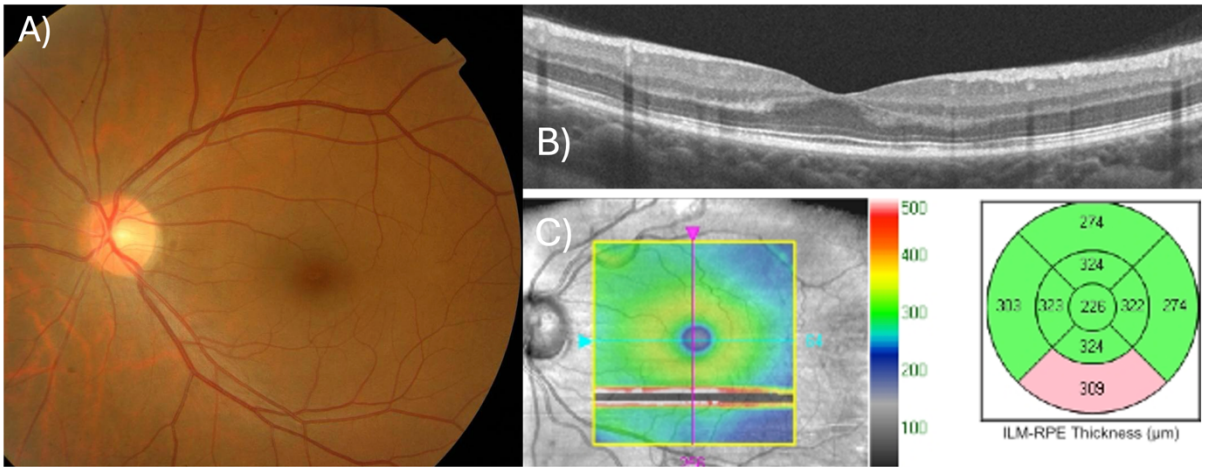


Figure 2.2. Left CRVO with vision of 6/120 (20 log MAR letters). A) Colour retinal photograph demonstrating dilated tortuous veins, dense intraretinal haemorrhages, swollen optic disc and gross cystoid macular oedema. B) OCT raster at presentation demonstrating gross macular oedema. C) Response to treatment as seen on the OCT raster after one intravitreal injection of a VEGF inhibitor.

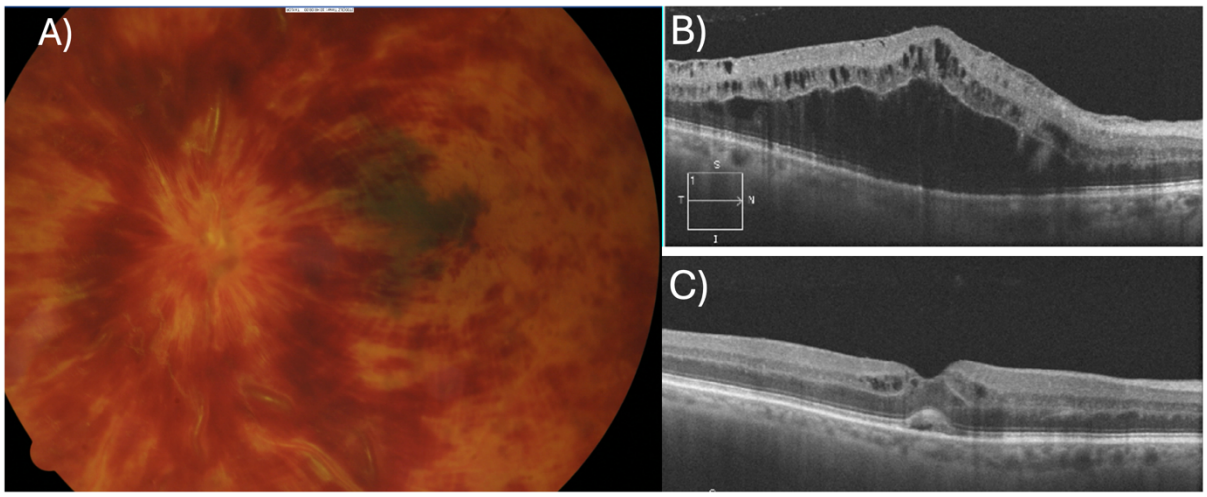


Figure 2.3. Right supero-temporal BRVO with Vision of 6/60 (35 log MAR letters). A) Colour fundus photograph demonstrating dense intraretinal haemorrhages, a few cotton wool spots and cystoid macular oedema. B) OCT raster at presentation. C) Response to treatment as seen on the OCT raster after one intravitreal injection of a VEGF inhibitor.

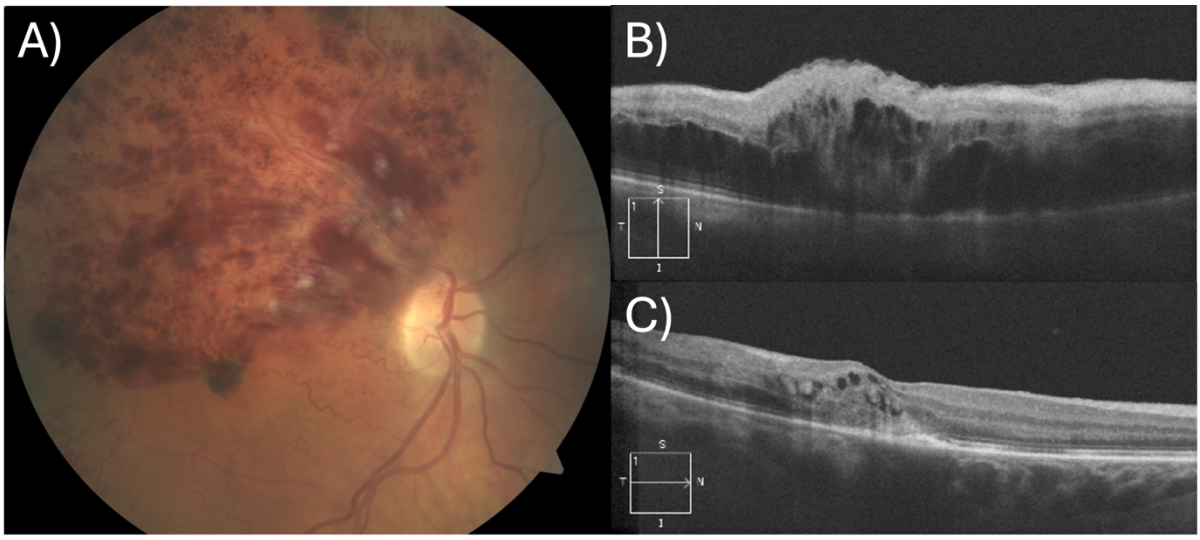


Figure 2.4. Right inferior ischaemic HRVO. A) Colour retinal photography demonstrating cotton wool spots, dilated tortuous inferior retinal veins, intraretinal haemorrhages, inferior optic disc swelling and cystoid macular oedema. B) Fundus Fluorescein Angiogram (FFA) demonstrating extensive capillary non-perfusion and blockage from retinal haemorrhages taken 32 seconds after sodium fluorescein has been injected intravenously.

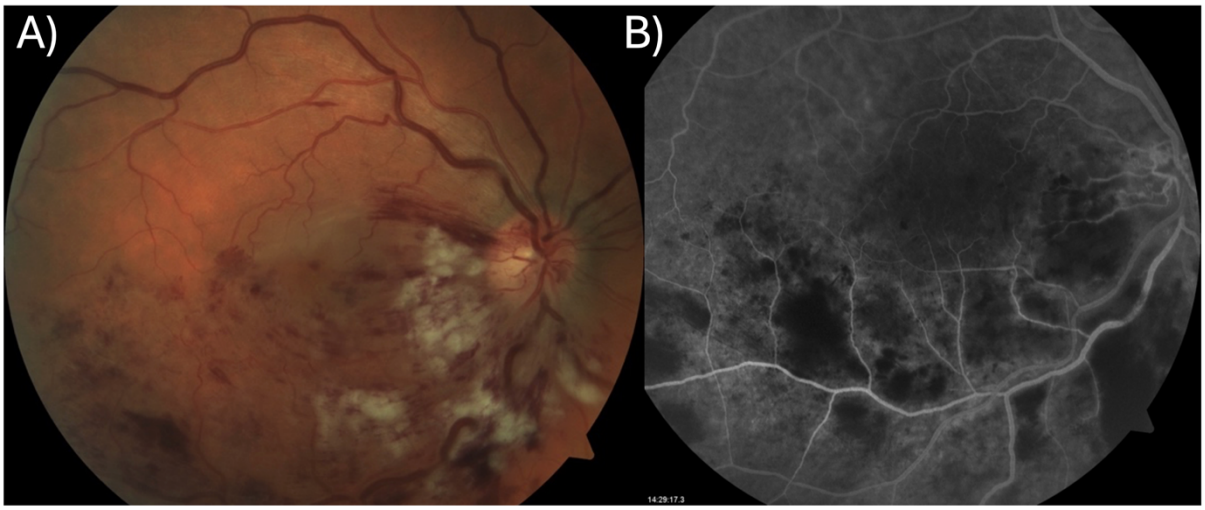
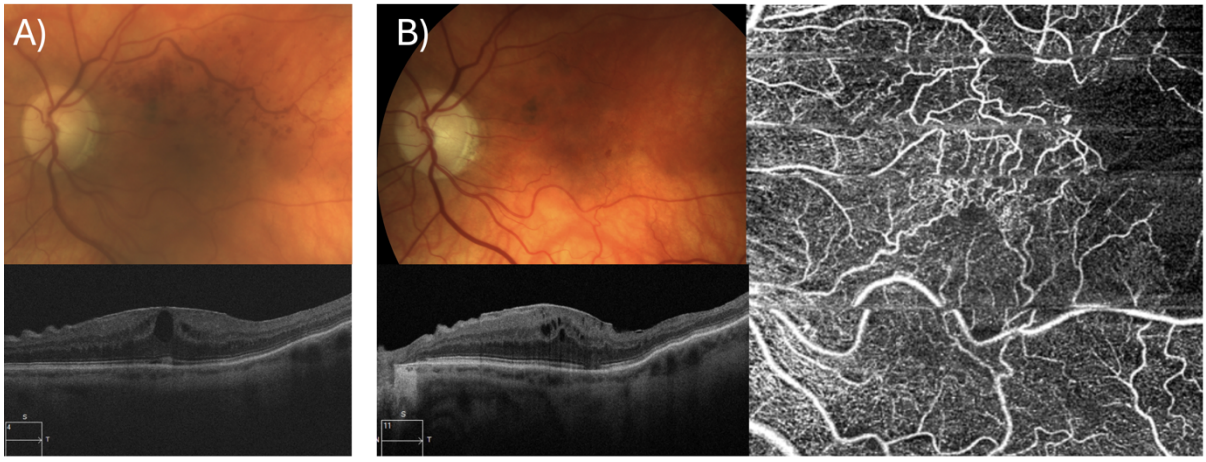


Figure 2.5. Superior macular BRVO. A) Colour retinal photography at presentation demonstrating retinal haemorrhages within the arcades, macular OCT with intra-retinal fluid and some epiretinal membrane. B) Colour retinal photography showing significant reduction in retinal haemorrhages following 2.5 years of treatment with VEGF inhibitors, however ongoing treatment was required to maintain clinical outcomes including the stability of VA and a relatively dry macula. OCT demonstrates some persistent macular oedema and epiretinal membrane. OCT angiogram demonstrates vascular changes in the region of branch retinal vein occlusion with the development of some collateral vasculature.



2.1.5 Natural History and Complications

Permanent visual impairment can occur with RVO due to chronic macular oedema or from neovascular complications. Though spontaneous improvement can eventually occur in RVO, any period of disruption to the normal macular architecture and function caused by oedema can lead to irreversible damage even after if it later subsides. Neovascularisation (NV) threatens the eye, let alone vision, in the posterior segment, either as NV elsewhere (NVE) or at the optic disc (NVD), from vitreous hemorrhage or tractional retinal detachment due to fibrovascular proliferation. Anterior segment NV, particularly in CRVO either at presentation or during follow-up, at the iris (NVI) and in the angle (NVA) can cause painful loss of vision due to neovascular glaucoma (NVG).

Spontaneous improvement in CRVO can occur due to the development of collateral circulation (an opto-ciliary shunt) or possible recanalisation of the occluded central vein (Green et al., 1981). Similarly, BRVO and HRVO can improve via collateral circulation that

decompresses the congested venous circulation via the retinal capillaries that cross the median raphe to the unaffected retinal venous system. HRVO shares with CRVO the potential for an optociliary shunt or uniquely may develop a collateral circulation to the adjacent unaffected hemiretinal vein (Chopdar, 1982; Green et al., 1981; McAllister & Barry, 1991).

The Central Vein Occlusion Study group (CVOS_group., 1997) identified the association between initial VA and final VA in CRVO, categorised levels of ischaemia (ischaemic or non-ischaemic CRVO). An ischaemic CRVO was defined by > 10-disc areas of non-perfusion on FFA (55-degree view). They found ischaemia predicted the natural history of CRVO. Only 10% of ischaemic CRVO eyes achieved visual acuity of ≥ 6/120. Most (83%) indeterminate cases were recognised as ischaemic once the haemorrhages had cleared. The CVOS group found that neovascular complications in the iris or angle (NVI/NVA) occurred in few (10%) of the non-ischaemic CRVOs, compared to a third (35%) of ischaemic or indeterminate eyes.

Hayreh et al (Hayreh, Klugman, Beri, Kimura, & Podhajsky, 1990) described six routine clinical tests that differentiated ischaemic (30%) from non-ischaemic (70%) CRVO (visual acuity, visual fields, relative afferent pupillary defect (RAPD), electroretinography (ERG), ophthalmoscopy and fluorescein fundus angiography). Identifying ischaemia was important as it was predictive of neovascular complications in CRVO, which include NVI in 49%, NVA in 37%, NVG in 29%, NVE in 9% and NVD in 6% within 6 months onset (Hayreh & Zimmerman, 2012). In contrast, eyes with non-ischaemic CRVO develop neovascular complications rarely (1.3%). Nevertheless, one third of eyes that were non-ischaemic at presentation became ischaemic over 3 years, illustrating the need for follow-up (McIntosh et al., 2010).

Rogers et al reviewed 24 eligible studies with natural history data in 1608 eyes with BRVO (S. L. Rogers et al., 2010). Variable levels of spontaneous improvement were reported for up

to 2 years, but rarely did vision improve beyond 6/12. This was despite one included study demonstrating resolution of macular oedema in 41% within 7.5 months of onset of the occlusion (Shroff, Mehta, Arora, Narula, & Chauhan, 2008). The Branch Vein Occlusion Study identified that a threshold of > 5-disc areas of ischaemia on FFA predicted posterior segment neovascularisation (BVOS_group, 1986). The SCORE Study Report #11 reported 8.8% of eyes with BRVO were complicated by neovascularisation (NVE or NVD) over 3 years (Chan et al., 2011).

2.1.6 Management of RVO

A dramatic shift has occurred in the management of RVO over the past two decades influenced mostly by the invention of intravitreal therapies. Currently management involves a proactive approach involving regular injections of VEGF inhibitors guided by visual acuity, clinical examination and OCT scanning. This largely replaced what had been a reactive approach involving observation and retinal laser guided by FFA (ASRS, 2022). Holistic management continues to include consideration of associated systemic disease (Yau, Lee, Wong, Best, & Jenkins, 2008), PRP and sectoral laser remained standard of care for neovascular complications (BVOS_group, 1986; CVOS_group, 1995b), while intravitreal steroids because of their limited efficacy and side effect profile have a second-line role in select eyes according to treatment guidelines in eyes unresponsive to VEGF therapy (Braithwaite, Nanji, Lindsley, & Greenberg, 2014; Flaxel et al., 2020; Schmidt-Erfurth et al., 2019; Shalchi et al., 2020).

A short review of clinical trial evidence regarding the safety and efficacy of available local treatments for RVO follows. The existing real-world evidence is then reviewed. Particular emphasis throughout is placed on the three main VEGF inhibitors widely available in routine care over recent years – ranibizumab, aflibercept and bevacizumab.

2.2 Trial Evidence Supporting the Management of RVO

2.2.1 Retinal Laser in RVO

The Central Vein Occlusion Study (CVOS) and Branch Vein Occlusion Study (BVOS) groups provided evidence in the 1980-90's of the benefits to patients with CRVO and BRVO of regular monitoring for neovascularisation (NV), for laser photocoagulation to induce regression of NV once detected and for focal/grid laser as an effective treatment for macular oedema only in BRVO (BVOS_group, 1984, 1986; CVOS_group, 1993, 1995a, 1995b; CVOS_group., 1997).

The CVOS group developed a protocol of periodic review specific to CRVO (CVOS_group., 1997), watching and waiting for neovascular complications (CVOS_group, 1993), to be followed swiftly by the application of panretinal photocoagulation (PRP) in the presence of NVI that induced prompt regression in 56% and eventual stabilization in close to 90% of eyes (CVOS_group, 1995b). In reality, most clinicians have tended to perform PRP laser when any NV is detected in CRVO rather than waiting for NVI as it can be so problematic. PRP laser remains the standard of care for NV due to CRVO. The CVOS group failed to show benefit from macular grid laser in CRVO (CVOS_group, 1995a).

The BVOS group provided the evidence for sectoral photocoagulation in BRVO that remains the standard of care for inducing regression of neovascularisation (BVOS_group, 1986). The BVOS group also found grid or focal macular laser for centre-involving macular oedema significantly increased the likelihood of VA improving by ≥ 10 letters in BRVO compared with observation (BVOS_group, 1984), keeping in mind that some spontaneous improvement is expected in most BRVO eyes followed for up to 2 years, though rarely does VA improve beyond 6/12 without treatment (S. L. Rogers et al., 2010). Nevertheless, focal laser became

standard of care for macular oedema due to BRVO, at least until intravitreal therapies revolutionised management years later.

The Laser Chorio-Retinal Anastomosis (L-CRA) group provided RCT evidence (N=58) supporting the combination of L-CRA and ranibizumab compared with ranibizumab monotherapy in reducing the frequency of injections required over 24 months in non-ischaemic CRVO (McAllister, Smithies, Chen, Mackey, & Sanfilippo, 2018, 2021). After the initial 6 monthly injections of ranibizumab, the L-CRA arm required a mean (95% CI) of 3.2 injections of ranibizumab (2.5-3.8) compared with 7.1 injections (6.0-8.0) in the monotherapy arm of the trial. The mean CST was significantly lower (P = 0.01) in the L-CRA arm compared with the monotherapy arm at 24 months. The L-CRA treatment has not been widely adopted because of potential for adverse outcomes requiring vitrectomy including early macular traction or vitreous haemorrhage.

2.2.2 Intravitreal Steroids for RVO

2.2.2.1 Intravitreal triamcinolone (IVTA) for RVO

Use of “off-label” intravitreal triamcinolone (IVTA) for macular oedema due to RVO was reasonably widespread from 2002 onwards based on limited evidence (Greenberg, Martidis, Rogers, Duker, & Reichel, 2002; Ip & Kumar, 2002; Jonas, Kreissig, & Degenring, 2002). The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) group reported in 2009 the efficacy and safety of 1mg IVTA or 4mg IVTA (Allergan Inc, Irvine, California; 4-mg brand name, Trivaris) compared with standard of care in near identical studies of non-ischaemic CRVO (N=271) and BRVO (N=411) (Ip et al., 2009; I. U. Scott et al., 2009). In the CRVO study, the 1mg and 4mg IVTA groups had 5x higher likelihood of achieving the primary outcome of ≥ 15 letter improvement 12-months from baseline compared with observation, but in the BRVO study neither the 1mg nor the 4mg doses were associated with significant benefit compared with focal laser. The SCORE group also described the

increased risks of cataract and glaucoma in eyes treated with IVTA (Aref et al., 2015; Ip et al., 2009; I. U. Scott et al., 2009).

2.2.2.2 Dexamethasone Intravitreal Implant for RVO - Trials

The dexamethasone implant was designed to deliver steroid more smoothly over time than IVTA while causing IOP elevation and cataract possibly at lower rates than for IVTA. The Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion with Macular Edema (GENEVA) trials assessed the safety and efficacy of two doses of a dexamethasone eluting implant (0.7, 0.35 mg) compared with sham in the treatment of macular oedema due to BRVO and CRVO (Haller et al., 2010). The primary outcome of the GENEVA studies was the proportion of eyes with ≥ 15-letter improvement in best-corrected visual acuity (BCVA) from baseline. The eyes randomised to dexamethasone groups initially performed significantly better than those in the sham arm, however no significant difference in the primary outcome was found at 180 days after implantation (difference, 6.5% [95% CI: -0.9% to 13.9%] (Haller et al., 2010). A saw-tooth pattern in mean CST demonstrated recurrence of macular thickening prior to the opportunity for retreatment at 6-month intervals. A study in monkeys, that analysed the pharmacokinetic profile of the dexamethasone implant, found concentrations of dexamethasone in both the retina and vitreous after implantation were high from 7 to 60 days but were low from 90 to 210 days (Chang-Lin et al., 2011). Nevertheless, approval was granted for the 0.7mg dose (Ozurdex® - Allergan Inc., Irvine, CA, USA) with ≥ 6-monthly retreatment intervals as initial therapy for RVO in Europe, while in Australia approval was granted only in eyes that were unresponsive to VEGF inhibitors, that were pseudophakic eyes or were scheduled for cataract surgery, but retreatment was permitted with ≥ 4-monthly intervals.

2.2.3 Vascular Endothelial Growth Factor Inhibitors

2.2.3.1 Ranibizumab for RVO – Trials

Ranibizumab (Lucentis; Genetech, Inc., South San Francisco, CA, USA) is a fragment of bevacizumab produced specifically for ophthalmic use by recombinant deoxyribonucleic acid (DNA) technology within Escherichia coli cells of the 49kDa humanised monoclonal antibody fragment antigen-binding (Fab) fragment. Ranibizumab is thought to penetrate the retina better, have a higher affinity for VEGF-A and a shorter systemic half-life than bevacizumab (Ferrara, Damico, Shams, Lowman, & Kim, 2006). Ranibizumab was the first VEGF inhibitor to be assessed in large-scale seminal RCTs for the treatment of MO secondary to RVO.

The 6-month BRAVO (BRVO, N=397 [incl. 17% HRVO]) (Campochiaro et al., 2010) and CRUISE (CRVO, N=392) (Brown et al., 2010) studies were large phase III multicentre randomised controlled trials that demonstrated monthly ranibizumab, both at 0.3mg and 0.5mg dosages, was rapid and highly effective in improving VA and reducing cystoid macular oedema (CMO) due to RVO when compared to sham. The mean baseline VA and CST in BRAVO were 53 letters and 551µm, in CRUISE they were 48 letters and 685µm. The mean 6-month changes in VA achieved with ranibizumab dosed at 0.3mg/0.5mg were in BRVO +16.6/+18.3 letters compared with sham +7.3 letters ($P < 0.01$); and in CRVO +12.7/+14.9 letters compared with sham +0.8 letter ($P < 0.01$). The largest changes in VA occurred in eyes with the lowest baseline VA. Three-line improvements in VA occurred in 55% of BRVO and 46% of CRVO treated eyes compared with only 29% and 17% of sham eyes respectively. Rescue focal laser was permitted in the 6-month BRAVO trial, delivered to 55% of sham eyes but only 19% of ranibizumab treated BRVO eyes ($P < 0.01$). The anatomical outcomes were significantly better in the combined ranibizumab dosage arms including mean changes in CST in BRVO of -330 μm and in CRVO of -430 μm compared with sham of -158 and -168 μm, respectively ($P < 0.01$, $P < 0.01$).

Participants of the BRAVO and CRUISE studies were subsequently offered enrolment in observational extension studies using ranibizumab on a flexible regimen from 6 to 12 months (Brown et al., 2011; Campochiaro et al., 2011). There was some controversy in offering treatment to eyes previously given sham injections. On one hand, the natural history or standard of care data in sham eyes ended at 6 months, on the other hand, the impact of treatment delay was highlighted by the muted outcomes in the sham groups after they eventually received ranibizumab.

Participants previously treated monthly in the BRAVO and CRUISE studies maintained visual gains through 12 months despite shifting to a *pro-re-nata* regimen (PRN) with fewer injections delivered from 6 to 12 months (BRVO: 2.7 / 2.8 injections, CRVO: 3.8 / 3.3 injections). Interestingly, an immediate drop in mean VA occurred between month 6 and 7 as many eyes did not satisfy retreatment criteria at the first PRN visit (Brown et al., 2011; Campochiaro et al., 2011). The deterioration was only a temporary setback, with impressive 12-month mean changes in VA in BRVO of +18.3/+16.4 letters and in CRVO of 13.9/+13.9 letters in the 0.5 mg and 0.3 mg groups, respectively. Participants initially treated with sham had rapid and highly effective reductions in CST once they were eligible to receive ranibizumab, however the detrimental effect of delaying treatment by 6 months was evident in the mean visual outcomes at 12 months in both CRVO: +7 letters and BRVO +12 letters after a mean of 3.7 and 3.6 injections respectively from month 6 to 12.

Similar small RCTs supported the evidence from the BRAVO and CRUISE studies regarding the safety and efficacy of ranibizumab in RVO compared with sham. An Australian RCT randomised 36 eyes with BRVO to a protocol like BRAVO however sham was maintained through 12 months (M. H. Tan et al., 2014). Despite very frequent focal laser in the sham group at 13 or 26 weeks (68.4% and 50%) compared with the ranibizumab group (6.7% and 8.3% [$P = 0.0004$ and $P = 0.04$]), the authors found 12-month outcomes with ranibizumab were far better than with sham/laser (VA: +12.5 vs. -1.6 letters [$P = 0.032$], CST -362µm vs.

-176 µm [*P* = 0.025]). A Norwegian study (0.5mg Ranibizumab 1:1 Sham, N=32, 6 months) had a design that was like a condensed version of CRUISE study – three ranibizumab injections given monthly led to outcomes that paralleled the early results seen in the CRUISE study, however, after switching to a PRN regime at 3 months, rather than at 6 months in the CRUISE study, outcomes eroded (Kinge et al., 2010).

The open label extension HORIZON study observed over three quarters of the BRAVO and CRUISE participants into their second year of treatment using PRN ranibizumab (0.5mg).(Heier et al., 2012) The authors reported a generalised loss of vision in BRVO of -0.9 (sham/0.5 mg), -2.3 (0.3/0.5 mg) and -0.7 (0.5 mg) and in CRVO of -4.2 (sham/0.5 mg), -5.2 (0.3/0.5 mg) and -4.1 (0.5 mg). The authors of HORIZON concluded that patients with RVO, particularly those with CRVO, were prone to losing vision when they were reviewed less frequently while treated with a flexible regimen. They advocated for more frequent follow-up than every 3 months.

The RETAIN study reported limited longer-term outcomes in a small subset (8%) of the original BRAVO / CRUISE cohorts (N=66), raising concerns of selection bias towards patients satisfied with the outcomes of their treatment (Campochiaro, Sophie, et al., 2014). Participants in RETAIN tended to be either on active treatment or had not required treatment since participating in the RCTs. Nevertheless, excellent outcomes were maintained through a mean of 49 months, after year 4 there was still a requirement for ongoing injections of ranibizumab in 46% of eyes with BRVO and 56% of eyes with CRVO, final VA ≥ 6/12 was maintained in 80% of eyes with BRVO and 44% with CRVO. Early CRVO response to treatment based on OCT parameters at 3 months predicted outcomes in a separate report (Bhisitkul, Campochiaro, Shapiro, & Rubio, 2013).

CAPTURE (CRVO=40, BRVO=50) was a single-centre long-term prospective study in a subset of participants from ranibizumab trials for RVO (Iftikhar et al., 2019). Unlike the

RETAIN study that recruited 8% of BRAVO and CRUISE participants, the representative nature of the cohort in CAPTURE was likely strengthened by enrolment of 90 of 150 eyes that had participated in the BRAVO and CRUISE studies at a single centre. The study described how the impressive gains in VA achieved during the early phase of therapy for RVO using VEGF inhibitors eroded over a mean follow-up in CRVO of 78 months and in BRVO of 58 months. The authors surmised that recurrent bouts of oedema likely caused irreversible deterioration in visual potential even if subsequent treatment was effective in returning macular thickness to normal levels. They advocated for consistent control of MO to achieve optimal outcomes using VEGF inhibitors for RVO.

The 15-month multicenter, randomised SHORE study (N=162) was designed to test if the mean decrease in VA at month 7 reported in the BRAVO and CRUISE studies when all eyes were switched from monthly to PRN at month 6 could be avoided by being more selective with which eyes were transitioned to PRN (Campochiaro, Wykoff, et al., 2014). The study design resembled the first 6 months of BRAVO and CRUISE, but eyes were subsequently randomised to either monthly or PRN *only* when stable. Eyes that were not randomised, continued monthly treatment including 15% that never met the stability criteria. By being selective, the PRN group (N=82) received half the number of injections of the eyes that continued monthly treatment (N=80) but with similar 15-month outcomes (PRN +19.7 letters, monthly +17.5 letters).

The RELATE study tested the hypotheses that laser may have an adjunctive role to VEGF inhibitors for BRVO and that a higher dose of ranibizumab may benefit particularly CRVO. Higher aqueous levels of VEGF had been found in eyes with CRVO than with BRVO (Campochiaro et al., 2009). The participants were not treatment-naïve to either VEGF inhibitors or steroid when randomised to 0.5mg or 2.0mg ranibizumab on a flexible regimen. Visual outcomes after 24 weeks were not significantly better with the higher dose of ranibizumab in either CRVO or BRVO, despite significantly greater reductions in CST in

CRVO when treated with the higher dose. The application of laser (scatter +/- grid) was not associated with resolution of macular oedema or improvement of visual outcomes, nor did it reduce the frequency of VEGF inhibitor injections in BRVO. In fact, the authors stated that laser aggravated the macular oedema in some patients in the study. This study was of a higher quality than other small uncontrolled studies at that time that suggested laser may have an adjunctive role in eyes receiving VEGF inhibitors for RVO (Rehak et al., 2014; Spaide, 2013).

The BRIGHTER study (BRVO, N=455) (Tadayoni et al., 2016) and CRYSTAL study (CRVO, N=357) (Michael Larsen et al., 2016) enrolled broad RVO cohorts, including eyes normally excluded from trials with peripheral or macular ischaemia. The BRIGHTER (BRVO) study found eyes randomised to either ranibizumab or ranibizumab +/- laser had similar outcomes at 6 months, but eyes receiving ranibizumab had far superior outcomes compared with those receiving laser alone (6-month Change in VA, mean: +14.8, +14.8, +6.0 letters; $P < 0.001$, both). The BRIGHTER study at 24 months found neither macular ischaemia nor adjunctive laser had any significant effect on VA outcomes or treatment frequency with ranibizumab for BRVO (Tadayoni et al., 2017). The CRYSTAL study of a broad population of patients with CRVO found ranibizumab 0.5 mg delivered according to VA stabilization criteria for up to 12 months (Michael Larsen et al., 2016) and 24 months (M. Larsen et al., 2018) led to significant BCVA gains, including in eyes with macular ischaemia at baseline. A mean of 13.1 ranibizumab injections were delivered over 24 months. Particularly short or long disease duration prior to treatment commencement had a modest effect upon outcomes at 24 months (< 3 months: +13.2 letters, > 9 months: +10.5 letters).

2.2.3.2 Aflibercept for RVO – Trials

Aflibercept 2mg (Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA and Bayer HealthCare Pharmaceuticals Inc., Berlin, Germany) is a 115kDa recombinant fusion protein

with high-affinity VEGF blockade, that acts as a soluble decoy receptor but also binds placental growth factor 1 and 2 (Holash et al., 2002).

The VIBRANT study (BRVO [HRVO], N=183) was a prospective, multicentre, double-masked, randomised, controlled phase 3 trial that evaluated the efficacy and safety of 4-weekly intravitreal aflibercept 2mg injections compared with sham / grid laser through 24 weeks (Campochiaro et al., 2015). At 24 weeks, significantly more eyes achieved the primary outcome of ≥ 15 letters gain in VA from baseline with monthly aflibercept compared with sham / laser alone (52.7% vs. 26.7%; P = 0.0003), mean change in VA and CST were also significantly greater with aflibercept than sham / laser (+17.0 vs. +6.9 letters and -280.5μm vs. -128μm; P < 0.0001, both).

VIBRANT study participants were subsequently offered enrolment in an observational extension using aflibercept 8-weekly from 24 to 52 months (Clark et al., 2016). Treatment commenced in the sham group after week 24 involving three monthly injections followed by 8 weekly injections. The delay in starting treatment in eyes in the sham arm affected outcomes. At 52 weeks, more eyes achieved ≥ 15 letters gains in VA from baseline with prompt than with delayed aflibercept (57.1% vs. 41.1%; P = 0.03), mean change in VA was significantly greater with prompt than with delayed aflibercept (+17.1 vs. +12.2; P = 0.0035) and central retinal thickness (CRT) reduced more with prompt than with delayed aflibercept (-283.9 μm vs. -249.3 μm; P = 0.021).

The COPERNICUS (N=189) study was a multicentre, double-blind, randomised, sham-controlled phase 3 trials that evaluated the efficacy and safety in CRVO of monthly aflibercept 2mg injections (N=115) compared to sham treatment (N=74) for 6 months, followed by monthly review and PRN aflibercept in all eyes thereafter through 2 years (Heier et al., 2014). At each of the 6-, 12- and 24-month endpoints, treatment with q4w / PRN aflibercept compared with sham / PRN led to a significantly higher proportion of eyes

achieving the primary outcome of ≥ 15 letters gain in VA from baseline (56.1% vs. 12.3%, 55.5% vs. 30.1% and 49.1% vs. 23.3%; all $P < 0.001$), higher mean changes in VA (+17.3 vs. -4.0 letters, +16.2 vs. +3.8 letters and +13.0 vs. +1.5 letters; all $P < 0.001$) and larger reductions in CRT (-457.2μm vs. -144.8μm; $P < 0.001$, -413.0μm vs. -381.8 μm; $P = 0.546$ and -390.0μm versus -343.3μm; $P = 0.366$). In the q4w / PRN group compared with the sham / PRN group, mean (SD) PRN injection frequency in the second 6 months was 2.7 ± 1.7 vs. 3.9 ± 2.0 and in the second year it was 3.3 ± 2.1 vs. 2.9 ± 2.0. The authors concluded that a small erosion of initial gains in VA in the q4w / PRN group occurred in step with decreased injection frequency while on a PRN regimen and that the delay in starting treatment in the sham / PRN group affected 2-year visual outcomes even though macular thickness outcomes were eventually similar to eyes that had received aflibercept from the outset.

The GALILEO (N=177) study (Ogura et al., 2014) was very similar to COPERNICUS in eyes with non-ischaemic CRVO. However, in GALILEO the sham treatment extended for longer (48 weeks), the study period was shorter (18 months) and review while on PRN treatment was half as frequent in the final 6 months (8-weekly) compared with COPERNICUS. At 6, 12 and 18 months, treatment with q4w / PRN aflibercept compared with sham / PRN aflibercept led to a significantly higher proportion of eyes achieving the primary outcome of ≥ 15 letters gain in VA from baseline (60.2% vs 22.1%, 60.2% vs 32.4%, 57.3% vs 29.4%; all $P < 0.001$), higher mean changes in VA (+18.0 vs. +3.3 letters, +16.9 vs. +3.8 letters and +13.7 vs. +6.2 letters; all $P < 0.01$) and larger reductions in CRT (-448.6μm vs -169.3μm; $P < 0.001$, -423.5μm vs -219.3μm; $P < 0.001$ and -389.4μm vs -306.4μm; $P = 0.11$). The q4w / PRN group during the PRN stage of treatment received a mean (SD) of 2.5 ± 1.7 injections in the second 6 months and 1.3 ± 1.1 injections in in the final 6 months. The authors concluded outcomes were reasonably well maintained after prompt treatment of CRVO using aflibercept however the 48-week delay in receiving aflibercept in the sham group had a

significantly detrimental effect on 18-month outcomes combined with the bimonthly rather than monthly PRN regimen in GALILEO trial.

CENTERA was an open-label, single arm, phase 4 clinical study that found aflibercept safe and effective when delivered frequently using a particularly proactive treat and extend regimen in a select cohort with MO secondary to CRVO (N=160) (Korobelnik et al., 2021). The mean 76-week change in VA was +20.3 letters, improving from a mean VA at baseline of 51.9 letters to 72.3 letters at 76 weeks, following a mean of 5.3 injections in the first 6 months, 3.9 in the second 6 months and 3.0 in the third 6 months. Mean CST had reduced to a mean of 265μm at 76 weeks. A smaller Australian trial had similar outcomes in 20 patients with CRVO using a similar proactive aflibercept treat and extend regimen over 18 months (O'Day et al., 2020).

2.2.3.3 Bevacizumab for RVO – Trials

Bevacizumab (Avastin; Genentech, South San Francisco, CA, USA/Roche, Basel, Switzerland) is a 149kDa full length humanised-mouse monoclonal IgG antibody binds and neutralises all isoforms of VEGF-A (Ferrara, Hillan, Gerber, & Novotny, 2004). Bevacizumab was designed to inhibit angiogenesis and was approved for metastatic colorectal cancer with listing on the Australian Register of Therapeutic Goods in 2005. It became and continues to be widely used "off label" in many centres around the world for reasons of access and economics. It is the only VEGF inhibitor on the World Health Organisation list of essential medicines (WHO, 2019). The early availability of inexpensive compounded bevacizumab along with an impression of similar efficacy amongst VEGF inhibitors made it a popular "off-label" treatment for many years in lieu of trial evidence directly supporting its use in RVO, though the non-inferiority of bevacizumab and approved VEGF inhibitors was demonstrated some years later in RVO (Hykin et al., 2021; Narayanan et al., 2016; Rajagopal et al., 2015; I. U. Scott, VanVeldhuisen, Ip, Blodi, Oden, Awh, et al., 2017; Vader et al., 2020).

Small trials reported the benefits of bevacizumab in both improving VA and reducing macular thickness compared with laser or observation in BRVO (N=30) (Russo et al., 2009) and in CRVO (N=60) (Epstein, Algvere, von Wendt, Seregard, & Kvanta, 2012) around the same time that pivotal trials of ranibizumab for RVO were being reported. A small prospective single-centre trial (N=57) in 50% ischaemic / 50% non-ischaemic eyes with CRVO (HRVO) reported exceptional outcomes with double the usual dose of bevacizumab (2.5mg) on a flexible regimen over 3 years in Romania (Călugăru & Călugăru, 2015). The ischaemic / non-ischaemic eyes with mean baseline VA of 18 / 60 letters improved by a mean of +27 / +17 letters after a mean of 9 “double dose” bevacizumab injections over 3 years.

2.2.3.4 Non-Inferiority of VEGF inhibitors for RVO - Trials

The CRAVE trial (RVO, N=98) found no difference in mean change in CST at 6 months (the primary outcome) in eyes randomised to either monthly bevacizumab (mean, -212.6μm) or monthly ranibizumab (-243.8μm; P = 0.72), mean change in VA was also similar at 6 months (Rajagopal et al., 2015). Non-inferiority specifically in BRVO of ranibizumab and bevacizumab was reinforced by the MARVEL trial (BRVO, N=75) using a flexible regime from the outset and monthly review (Narayanan et al., 2016). Treatment criteria were proactive yet a mean of only 3 injections were given in the first 6 months. Nevertheless, visual outcomes were excellent and similar for both drugs even though reductions in CST were modest at 6 months (Report 1: Bevacizumab +15.6 letters / -165 μm was non-inferior to Ranibizumab +18.1 letters / -177 μm). Report 2 of the MARVEL trial (Narayanan et al., 2016) covered the subsequent 6 months when patients with BRVO were review bimonthly and grid laser was offered in addition to very few PRN injections from month 6 to 12 (mean, 0.3+/-0.6 injections). Mean visual acuity was maintained through from 6 to 12 months but rescue macular laser was delivered to more bevacizumab eyes (20/38 [53%]) than ranibizumab eyes (11/37 [30%]; P = 0.06).

The SCORE2 (N=362) randomised clinical trial found bevacizumab and aflibercept non-inferior when delivered monthly to non-ischaemic CRVO (incl. HRVO) in improving BCVA at 6 months (+18.6 and +18.9 letters, respectively) (I. U. Scott, VanVeldhuisen, Ip, Blodi, Oden, Awh, et al., 2017). The mean changes in CST favoured aflibercept by almost 50μm however it was not significant ($P = 0.83$), though 54% of eyes in the aflibercept group had resolution of MO compared with 29% in the bevacizumab group ($P < 0.001$) at 6 months.

The SCORE2 cohort was followed for up to 5 years contributing to multiple subsequent analyses. Early findings identified younger age and lower baseline visual acuity (VA) as predictors of greater VA improvement at six months (I. U. Scott, VanVeldhuisen, Ip, Blodi, Oden, King, et al., 2017) and described the impact of CRVO on vision-related function (I. U. Scott, Figueroa, et al., 2017). At 12 months, eyes that initially responded well showed similar VA outcomes whether continued on monthly or PRN regimens (I. U. Scott et al., 2018). Subsequent analyses explored treatment modifications in eyes with poor initial response, including switching from aflibercept to dexamethasone and from bevacizumab to aflibercept (Ip et al., 2019). Other studies found associations between VA improvement and clearance of haemorrhage (Hendrick et al., 2021) and examined early outcomes at 3 months (Khurana et al., 2021), including fluctuations in macular thickness (I. U. Scott, Oden, VanVeldhuisen, Ip, & Blodi, 2022b) and IOP related events (Aref et al., 2021).

Comparative analyses reported similar 24-month outcomes in patients with HRVO versus CRVO despite differing baseline characteristics (I. U. Scott, Oden, VanVeldhuisen, Ip, & Blodi, 2022a). At five years, outcomes were presented for eyes completing long-term follow-up (I. U. Scott, VanVeldhuisen, Oden, Ip, & Blodi, 2022). Factors associated with discontinuation of therapy before five years included younger age, African American race, and complete resolution of macular oedema (I. U. Scott, Oden, VanVeldhuisen, Ip, & Blodi, 2023a). Additional studies addressed the cost-utility of treatments (Kymes et al., 2023), the temporal relationship between CST and VA during therapy (I. U. Scott, Oden,

VanVeldhuisen, Ip, & Blodi, 2023b) and the correlation of non-fluid OCT changes with visual function at month 60 (Ip, Scott, VanVeldhuisen, Oden, & Blodi, 2024). Finally, early anatomical response—specifically a thin or thick retina at month 1—was found to predict 2-year visual outcomes (I. U. Scott, Oden, Ip, VanVeldhuisen, & Blodi, 2024).

The SCORE2 group reported 5-year outcomes in eyes with non-ischaemic CRVO (HRVO) after commencing aflibercept or bevacizumab. Data were available through 5 years in 45% (150/330) (I. U. Scott, VanVeldhuisen, et al., 2022). The 5-year completers received around 26 injections, this included 10 injections by protocol in the first year and 16 injections in the next 4 years at the investigator's discretion. Two-thirds of the completers received treatment in the 5th year. The mean BCVA in completers was +13.5 letters from baseline at 5 years. In non-completers, the 5-year change in BCVA was predicted by longitudinal mixed effects models to impute outcomes of +8.4 letters based on similar eyes with data available. Visual and anatomical outcomes were similar after commencing bevacizumab or aflibercept. There were three cases of endophthalmitis, one during the first year (0.3% of patients) and 2 (0.8% of patients) during years 2 to 5.

The Bevacizumab to Ranibizumab in Retinal Vein Occlusions study was a multicentre, randomised, double-masked, clinical trial in 277 eyes with BRVO or CRVO (including HRVO) that found bevacizumab non-inferior to ranibizumab over 6 months with monthly injections (bevacizumab +15.3 letters / -287μm vs. ranibizumab +15.5 letters / -301μm; Change in VA: non-inferior / CST: P = 0.69) (Vader et al., 2020). There were more intraretinal cysts at 6 months in the bevacizumab than ranibizumab group (P = 0.015). In eyes with better baseline VA (≥ 63 letters), the changes in VA were not non-inferior with the bevacizumab treated eyes underperforming compared with ranibizumab treated eyes.

The LEAVO was a large RCT that reported non-inferiority of ranibizumab to aflibercept but could not conclude bevacizumab was non-inferior to ranibizumab for CRVO (N=463) in eyes

with VA between 19 and 78 letters in the United Kingdom (Hykin et al., 2021). Four injections were given monthly followed by a protocol defined flexible regimen with monthly review. Randomisation is generally enough to ensure baseline comparability between groups (Elkins, 2015). However, the baseline CST appeared particularly high in the ranibizumab group of the LEAVO study (mean [SD], 731.3 µm [227.6]) which means they may have had greater potential for improvement compared with the aflibercept and bevacizumab groups (673.2 µm [189.4] and 676.1 µm [207.0], respectively). The analysis of non-inferiority between agents involved adjustment for baseline VA but there was no mention of adjustment for any baseline CST differences and the primary outcome was unadjusted. The concern being that having more eyes with severe disease in the ranibizumab group of the LEAVO study may have impacted the primary outcome of unadjusted 100-week mean (SD) change in VA and the unadjusted mean (95% CI) changes in CST in the study (Bevacizumab: +9.8 letters [21.4] and –334 µm [–374, –293]; Ranibizumab: +12.5 letters [21.1] and –405 µm [–450, –360]; Aflibercept: +15.1 letters [18.7] and –378 µm [–412, –343]). The mean number of injections in the bevacizumab group was 11.5, in the ranibizumab group 11.8 and in the aflibercept group 10.0 injections over 100 weeks.

2.2.4 Summary of Trial Evidence

The trials regarding VEGF inhibitors for MO due to RVO describe the outstanding safety and efficacy of frequent intravitreal injections of ranibizumab, aflibercept or bevacizumab delivered to select cohorts following a strict protocol. A high burden of treatment involving around 9 or more injections in the first year when delivered promptly led to roughly +12 to +20 letter gains in VA. Outcomes were however vulnerable to decay particularly in eyes with CRVO when adopting a PRN regimen either too early, injudiciously or with subsequent 3-monthly reviews. Some evidence suggests potential for good longer-term outcomes in RVO

when macular oedema is well controlled likely irrespective of baseline ischaemia or choice of agent.

2.3 RWE Supporting VEGF inhibitors in RVO

2.3.1 Retrospective case series

The body of real-world evidence regarding VEGF inhibitors for RVO consists of many small retrospective case series mainly involving ranibizumab or bevacizumab (Ahn, Ahn, Woo, & Park, 2013; Braimah, Singh, Uplanchiwar, Mansour, & Chhablani, 2019; Brynskov, Kemp, & Sørensen, 2014; Buyru Özkurt, Akkaya, Aksoy, & Şimşek, 2018; Byun, Roh, Lee, & Koh, 2010; I. Chatziralli et al., 2018; Chen et al., 2010; Demir, Oba, Gulkilik, Odabasi, & Ozdal, 2011; Gokce, Sobaci, Durukan, & Erdurman, 2014; Hasegawa, Takahashi, et al., 2019; Hayashi et al., 2011; Hikichi et al., 2014; Hoeh, Ach, Schaal, Scheuerle, & Dithmar, 2009; Istek, Bursal, & Alagöz, 2014; Ito et al., 2015; Ivanovska Adjievska, Boskurt, Orovcanec, & Dimovska-Jordanova, 2017; Jaissle et al., 2011; Khan et al., 2017; J. Y. Kim & Park, 2009; M. Kim, Jeong, & Sagong, 2017; M. Kim et al., 2015; Kondo et al., 2009; Kornhauser et al., 2016; Lalinská, Krásný, Studený, & Veith, 2018; K. Lee, Jung, & Sohn, 2014; Lip et al., 2015; Miwa et al., 2017; Osaka et al., 2018; Ozkaya, Tarakcioglu, & Tanir, 2018; Rush, Simunovic, Aragon, & Ysasaga, 2014; Shiono et al., 2018; Siegel et al., 2012; Son, Kwak, Kim, & Yu, 2017; Thapa, Maharjan, & Paudyal, 2012; Tsagkataki, Papathomas, Lythgoe, & Kamal, 2015; J. K. Wang et al., 2016; Winterhalter et al., 2018; Wu et al., 2009; L. Zhao et al., 2015). They are limited to single centres or countries, typically requiring certain periods of follow-up for inclusion, reporting outcomes with VEGF inhibitors alone or in combination with laser, steroids or describe outcomes after switching of treatment. A meta-analysis of real-world BRVO studies in 2020 found that the visual and anatomic improvements were less impressive in the real-world than they were in RCTs (Ang et al., 2020). The meta-

analysis estimated the mean baseline VA and CST of 52.6 letters and 504 µm across all treatment groups and it estimated mean changes in VA of +13.1, +14.2 and + 14.0 letters at 6, 12 and 24 months respectively and mean changes in CST of -179 µm, -202 µm and -236 µm. Eyes received a mean of 2.7 injections at 6 months, 3.6 at 12 months and 5.2 injections at 24 months (Ang et al., 2020).

Some studies that focus on CRVO (Beutel et al., 2010; I. Chatziralli et al., 2017; Ehlken, Helms, Bohringer, Agostini, & Stahl, 2018; Iturralde et al., 2006; Khan et al., 2017; Kriechbaum et al., 2008; Lip et al., 2015; Prager et al., 2009; Priglinger et al., 2007; Rosenfeld, Fung, & Puliafito, 2005; Spooner, Fraser-Bell, Hong, & Chang, 2020; Vorum, Olesen, Zinck, & Storling Hedegaard, 2016; Wu et al., 2010) have reported that disorganisation of the retinal layers and poor renal function have a detrimental effect on outcomes using VEGF inhibitors (Babiuch et al., 2019; Madanagopalan & Kumari, 2018), that lower baseline VA with CRVO predicted larger gains in VA with VEGF inhibitors (Wai et al., 2017), that both ranibizumab and bevacizumab were effective in CRVO (N=76) and BRVO (N=124), though numerically greater reductions in CST occurred with ranibizumab (Vaz-Pereira et al., 2017) and have described greater reductions in CST in eyes with CRVO compared with BRVO when treated with bevacizumab and/or dexamethasone (Khan et al., 2017; Winterhalter et al., 2018).

One of the larger real-world retrospective case reviews by Lip PL et al (N=156) described 12-month outcomes of bevacizumab for chronic macular oedema (> 12 months) despite previous laser or IVTA in eyes with BRVO (N=100) or CRVO (N=56) in the UK (Lip et al., 2015). Treatment with a mean of 3.3 (BRVO) and 4.2 (CRVO) injections led to little or no change in mean VA over 12 months from baseline in eyes with CRVO (mean VA was stable at 6/36) and only a slight improvement in eyes with BRVO (mean VA improved from 6/24 to 6/20). The mean CRT improved from baseline in CRVO from 449 µm to 278 µm and in BRVO from 411 µm to 335 µm over 12 months.

One of larger treatment-naïve, single-centre, real-world studies described 24-month outcomes after receipt of at least one bevacizumab injection for treatment-naïve BRVO (N=105) in Japan (Hikichi et al., 2014). Follow-up was excellent (85%) at 24 months. Mean baseline VA and CST were typical of BRVO cohorts at 52 letters and 572μm. The overall frequency of injections appeared low (3.8 injections over 24 months), though adjunctive macular laser was also delivered in 26% of eyes. The authors hypothesized that the likely longer half-life of bevacizumab may have been responsible for comparable outcomes (+8 letters at 24 months) despite a more relaxed treatment regimen compared with the HORIZON ranibizumab extension study (+15 letters at 24 months) (Heier et al., 2012). Patients in the Japanese study and the HORIZON extension both received around 2 injections in the second year, but the key difference was treatment frequency in the first year. In the Japanese study a mean of 2 injections (+9 letters at 12 months) were delivered whereas patients that entered HORIZON had received a mean of 8.8 injections in BRAVO resulting in gains of +18.3 letters at 12 months (Brown et al., 2011; Heier et al., 2012).

The ECHO study was a relatively small retrospective review of medical records of patients treated in ten US centres with VEGF inhibitors for mostly treatment-naïve BRVO (N=95) or CRVO (N=70) (Jumper, Dugel, Chen, Blinder, & Walt, 2018). Inclusion required ≥ 3 injections and ≥ 6-month follow-up, however the subsequent follow-up was available in only 10% at 36 months. The primary endpoint of combined good vision (VA ≥ 6/12) and a dry macula (CST ≤ 250μm time domain, ≤ 300μm spectral domain OCT) was achieved in around half of eyes at some point in their available follow-up.

OCEAN was a larger multicentre study that monitored delivery of ranibizumab injections in routine care in naïve (72%) and non-naïve (28%) patients with RVO (57% unknown type, 27% BRVO, 16% CRVO) in Germany (N=744) (Callizo et al., 2019). Mean baseline VA was 52 letters. A mean of 6 injections were delivered per year for two years. The analysis focussed on half of the eyes that completed 12 months (380/744 [51%]) that improved by

+10.7 and less than a third that completed 24 months (232/744 [31%]) that improved by +11.8 letters from baseline. When the last observation was carried forward in eyes that had non-completed, the overall changes in VA were lower at 12 and 24 months (mean, +9.0 and +8.0 letters) to suggest outcomes in non-completers were less impressive.

Stallworth et al retrospectively reviewed outcomes in 476 eyes with a range of presentations of CRVO treated by 22 retina specialists at a single retinal centre in the US predominantly with bevacizumab with varying lengths of follow-up (Stallworth, Akshay, Constantine, Stinnett, & Fekrat, 2020). The study included treatment-naïve, non-naïve (predominantly pre-treated with bevacizumab), non-ischaemic and ischaemic eyes with CRVO including eyes with anterior segment neovascularisation (9.4% NVI, 6.1% NVA). The mean visual acuity was essentially unchanged in the first year following around 3 to 5 injections likely related to the inclusion of eyes with chronic macular oedema or anterior segment neovascularisation and also eyes that had already started treatment that would have already had the initial increase in VA that is usually seen with VEGF inhibitors.

The outcomes of a particularly proactive treatment protocol using aflibercept for CRVO were analysed retrospectively through 12 months in a UK hospital in 44 eyes (Eleftheriadou, Nicholson, D'Alonzo, & Addison, 2019). More injections were delivered in this study compared with other reports – a mean of 8 aflibercept injections in 12 months. The treatment-naïve CRVO cohort had baseline VA between 24-73 log MAR letters (mean, 44.7 letters) and included some eyes with peripheral (18%) or macular ischaemia (9%). The protocol involved monthly treatment with at least 3 doses of aflibercept (q4w) until stable, then patients were treated and extended up to a maximum interval of 12 weeks. Eyes that had no macular oedema 12 weeks after a previous injection were switched to a PRN regimen. The protocol suggested treatment be abandoned in eyes with no visual improvement or switched in eyes with little anatomical improvement to another VEGF inhibitor or to a dexamethasone implant. Thirty-three eyes (75%) were eligible for the 52-

week analysis, of which 50% achieved the primary efficacy endpoint of VA improvement greater than 15 letters from baseline. The mean changes in VA and CST from baseline were +15.1 letters and -312 μm. The authors concluded that outcomes approaching those reported in trials could be achieved in routine care with a mean of 8 injections for CRVO in the first year, but non-responders, switchers and non-completers were excluded.

A small (N=76) retrospective study compared outcomes using pro re nata (PRN) or treat and extend (TAE) ranibizumab regimens for RVO in Switzerland (Guichard, Xavier, Türksever, Pruente, & Hatz, 2018). Eyes were selected only if they had 12-month follow-up. A deterioration in outcomes appeared to occur after loading when transitioned to PRN that did not occur when transitioned to TAE which persisted through 24 months (24-month mean change in VA: PRN +10 vs. TAE +17 letters; P = 0.17).

Completers-only analyses have described outcomes of VEGF inhibitors for RVO at 3 or 5 years. (I. Chatziralli et al., 2018; Farinha et al., 2015; Spooner, Fraser-Bell, Hong, & Chang, 2019; Wu et al., 2022) The outcomes of these studies are of limited utility as they do not include and therefore account for any eyes that did not complete the study period. Nevertheless, a range of outcomes were reported in 3- to 5-year completers including mean changes in VA in BRVO between +1.6 to +15 letters, in CRVO between +6.9 to +15 letters and a mean of 5.9 to 28.4 injections over 5 years.

A Swedish single-centre study described five-year outcomes in 292 eyes with RVO that commenced treatment with either VEGF inhibitors or the dexamethasone implant (de Salles & Epstein, 2021). There was a preference for starting VEGF inhibitors for CRVO if baseline VA was lower. Over two-thirds of eyes that commenced dexamethasone were phakic, but there was no account of the development of cataract and/or surgery. Less than 10% of eyes had follow-up at 5 years and more than half of the dexamethasone treated eyes were lost to follow-up before 1 year. Last observation was carried forward in eyes that were switched or

lost to follow-up. The final visual outcomes were generally better in eyes that had commenced VEGF therapy (CRVO +0.2, BRVO +9.8 letters) rather than dexamethasone (CRVO -9.7, BRVO -2.1 letters; $P = 0.11$, $P < 0.05$). In eyes with follow-up, VEGF inhibitors were given 3 to 5 times per year and dexamethasone was delivered twice per year.

2.3.2 Data extracted from medical records and claims databases

A retrospective study using insurance claims data identified 26,669 patients with RVO that received either ranibizumab or dexamethasone between 2010 and 2014 in the US (Nghiem-Buffet et al., 2017). The included eyes (CRVO=1178, BRVO=1644) treated with ranibizumab (N=2822) or dexamethasone implant (N=365) required ≥ 12 months of follow-up before and after to confirm treatment-naivety and to compare treatment burden over 1 year. The study found one extra visit and 2 more injections were given in eyes receiving ranibizumab (mean, visits 7.2, injections 4.1) than dexamethasone (mean, visits 6.2, injections 1.8) in the first 12 months of treatment ($P < 0.001$ for both).

Data were extracted from the medical records in eyes with RVO (CRVO = 3577, BRVO = 5661) managed at 27 NHS (National Health Service) Trusts in the UK (Gale et al., 2020; Gale et al., 2021). Selection required baseline VA to be present, amongst other criteria. Though the numbers with 3-year follow-up may appear reasonably large compared with other real-world studies (CRVO=209, BRVO=246) they represent a tiny fraction of the original cohorts (6% and 4%). This needs to be kept in mind when the authors make conclusions regarding the sustained effectiveness of treatment (CRVO and BRVO, both +11 letters) and associated treatment burden (7-10 injections) through three years.

A study by Wecker, et al. retrospectively extracted dates of treatment and VA measurements from the medical records of eyes with various retinal diseases (N=2577) managed according to a PRN treatment protocol recommended by the German Ophthalmological Societies (Wecker et al., 2017). Data were available for 194 eyes with RVO (subtype not specified)

including 33 eyes (17%) at 5 years. Based on only 8, 18 and 7 eyes from the original cohort of 194 eyes the authors reported that by year 5, 24% of patients with RVO gained > 15 letters, 55% remained stable and 21% lost > 15 letters.

The Vestrum Health Retina Database analysed the association between treatment frequency and change in VA in RVO including eyes with 6-month data (15,613 eyes) and 12-month data (12,214 eyes) available (T. Ciulla, Pollack, & Williams, 2021). The study found a range of mean changes in VA occurred with increasing frequency of treatment in CRVO from +2.0 to +15.5 letters and in BRVO from +2.9 to +13.1 letters, but the eyes treated with increasing frequency had progressively lower baseline VA which may have confounded the association.

Two other studies using data from the American Academy of Ophthalmology IRIS® (Intelligent Research in Sight) registry involved RVO that have highlighted differences in the presentation and delivery of care based on age, race, laterality and gender (Haller, Tomaiuolo, Lucas, Yang, & Hyman, 2024; Li et al., 2022).

2.3.3 Prospective observational studies

LUMINOUS was a prospective, multi-indication, multi-centre, pharma-sponsored study observing ranibizumab outcomes (1 year) and safety (5 years) in the real-world setting from 463 practice centres around the world (Lotery et al., 2022; Pearce et al., 2020). Included eyes with treatment-naïve BRVO (N=326) had mean baseline VA of 49.2 letters. Follow-up was available in less than half (47%) at 1 year that had mean VA improvement of +11.9 letters with 5.0 injections. No new safety signals were detected through year 5. The study demonstrated larger gains in eyes with lower baseline VA. In the eyes with treatment naïve CRVO (N=327) the mean baseline VA of 40.6 letters improved by +10.8 letters with a mean of 5.4 injections in the 76% with follow-up available at 1 year, with no new safety signals through year 5. The study observed eyes normally not included in RCTs, including eyes with

a full range of baseline VA. The authors concluded that fewer injections in LUMINOUS likely affected outcomes compared with trials such as CRYSTAL (+12.3 letters) and CRUISE (+13.9 letters) studies.

The RETAIN and CAPTURE studies were prospective trial-like observational extension studies discussed earlier that provided limited longer-term outcomes data in a subset of patients previously enrolled in pivotal ranibizumab RCTs.

2.3.4 Summary of Real-world Evidence

The visual and anatomic improvements with VEGF inhibitors for RVO appear far less impressive in the real-world where fewer injections are delivered than in RCTs. Some studies reported impressive outcomes however they did so in completers that were treated very frequently. In alignment with trial evidence, the real-world evidence also suggests that the frequency of treatment in the first 6 to 12 months tended to determine the extent of visual improvement, and that subsequent relaxation of treatment frequency tended to erode what had been achieved, most markedly in eyes with CRVO. Other signals from real-world evidence suggested possible superiority of aflibercept over ranibizumab and bevacizumab and superiority of TAE over PRN. Conclusions in real-world studies were frequently made based on very small fractions of original cohorts with follow-up or measurements available for analysis.

2.4 Knowledge Gaps and Research Objectives

This section discusses knowledge gaps apparent after reviewing the existing trial and real-world evidence above. It describes the limitations of trial and real-world evidence and how using data from patient registries may improve the quality of RWE. This is followed by the development of a comprehensive research plan for this thesis.

2.4.1 Limitations of Existing RCTs involving VEGF inhibitors for RVO

Randomised clinical trials (RCTs) are designed to best suit their aims (De Lanerolle, Phiri, & Haroon, 2023). Strict selection criteria ensure that the randomly assigned treatment delivered by protocol is the only factor influencing outcomes. Upper limits on VA at inclusion ensure that patients that respond well have vision gains. Lower limits on VA likely exclude eyes with ischaemia. The aims of the pivotal Phase III trials regarding both ranibizumab and aflibercept in the treatment of MO due to RVO were to provide evidence of the safety and efficacy of those agents compared with standard of care (SOC) at the time (Brown et al., 2010; Campochiaro et al., 2015; Campochiaro et al., 2010; Heier et al., 2014; Ogura et al., 2014). That evidence supported approval of these agents by regulatory bodies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) or the Therapeutic Goods Administration (TGA) in Australia. There are, however, limitations on the generalisability of that trial evidence to patients in routine care.

The application of strict selection criteria in RCTs may improve the validity of the experiment, but each exclusion chips away at how representative the sample is of the target population. The participants in the CRUISE study (Brown et al., 2010) had ages ≥18 years, no RAPD, baseline VA of 25-70 letters, no > 10 letter improvement since screening, CST ≥ 250µm, no prior RVO or treatment (including VEGF inhibitor fellow eye [3 months], or systemically [6 months], no prior PRP or planned laser) and no AMD, DR, stroke or myocardial infarction (3 months). The BRAVO study excluded recent focal laser (4 months) (Brown et al., 2011). Other common exclusions include females of childbearing potential, uncontrolled glaucoma, ocular surgery (3 months) or planned (6 months), concomitant topical, subconjunctival or intraocular steroids, vitreomacular interface abnormalities, systemic medications known to be toxic to the lens (Vader et al., 2020). The SCORE2 trial excluded patients with significant blepharitis, presumably to reduce the risk of infection confounding outcomes (I. U. M. D. M. P. H. Scott et al., 2016).

Listing the selection criteria above is not to criticise what is an important part of trial design. It demonstrates how the results of RCTs cannot be directly generalised to patients managed in routine care. All these patients that were excluded by RCTs nevertheless develop RVO and have to be managed in routine clinical practice. Besides listed exclusions, many patients are under-represented in trial cohorts for a multitude of other reasons. These include racial or socio-economic reasons, inadequacy of informed consent or the ethical protection of "vulnerable groups". Some patients just tend to self-select out of participation anyway because of other illnesses, general frailty or because they are fearful (Affairs et al., 2023).

The advantages and disadvantages of applying strict selection criteria in a trial are best described with reference to SCORE2 (I. U. M. D. M. P. H. Scott et al., 2016). Unlike most of the trials regarding RVO, the highly select SCORE2 cohort were followed for up to 5 years which generated a huge body of subsequent reports aimed at informing best practice of RVO using VEGF inhibitors (Aref et al., 2021; Hendrick et al., 2021; Ip et al., 2019; Ip et al., 2024; Khurana et al., 2021; Kymes et al., 2023; I. U. Scott, Figueroa, et al., 2017; I. U. Scott et al., 2024; I. U. Scott, Oden, et al., 2022a, 2022b; I. U. Scott et al., 2023a, 2023b; I. U. Scott et al., 2018; I. U. Scott, VanVeldhuisen, Ip, Blodi, Oden, King, et al., 2017; I. U. Scott, VanVeldhuisen, et al., 2022). On the one hand, the strict selection criteria in SCORE2 suited the main aim of assessing non-inferiority of aflibercept and bevacizumab in non-ischaemic CRVO at 6-months, but on the other hand, the sample being so highly selected diminishes the generalisability of the subsequent reports to the broad population managed in routine care.

It is not only the difference in populations but the difference in treatment frequency that affects outcomes in routine care compared with trials. Few patients in real world practice will sustain the regimented frequency of treatment that was delivered to participants of RCTs. Trials are well funded and conducted within academic environments ensuring strict adherence to protocol and follow-up schedules. Treatment in routine care is more frequently

individualised, fewer support staff ensure adherence and persistence with treatment, significant burden falls on the patients and caregivers and there often the added financial pressure of paying for treatment. The pervasiveness of undertreatment no doubt contributes to the less impressive outcomes achieved in routine care compared with trials.

2.4.2 The Complementary Role of RWE

Real-world evidence (RWE) can be difficult to define. For example, the TGA defines RWE as "Data regarding the usage, or the potential benefits or risks, of a therapeutic good derived from sources other than traditional clinical trials" (Government). In other words, RWE encompasses everything but clinical trials; from database studies, patient and population surveys, patient chart reviews, observational cohort studies, pragmatic clinical trials and also studies that use registry data. Pragmatic clinical trials (PCTs) straddle the boundary between RWE and RCTs (explanatory trials) with pragmatism assessed in PCTs based on how close the eligibility, recruitment, setting, organisation and support systems, flexibility in treatment delivery adherence and follow-up reflect typical care delivery in routine practice (Ford & Norrie; Schwartz & Lellouch, 1967).

Real-world evidence may be of varying levels of quality but collectively contributes information regarding "effectiveness" of an intervention that complements the "efficacy" data of RCTs. Well-designed clinical outcomes ophthalmic registries can provide particularly high-quality data for analyses that describe the effectiveness of actual care being delivered (J. C. K. Tan, Ferdi, Gillies, & Watson, 2019). More frequently RWE suffers from poor quality of data, follow-up and study design that degrade its standing in the hierarchy of clinical evidence (Burns, Rohrich, & Chung, 2011).

RWE is generally regarded as less valuable than evidence from RCTs, though in some instances it can be superior. RWE may be better suited to studying rare and chronic conditions, in monitoring outcomes of sub-optimal care that would not be ethical to plan for

prospectively, outcomes of off-label or unanticipated use of approved treatments or when an existing treatment is being reconsidered. RWE can capture data regarding care delivery in larger populations, over longer periods and more economically than trials. It can also expose limitations of treatments otherwise proven successful in RCTs.

2.4.3 Limitations of existing RWE involving VEGF inhibitors for RVO

After reviewing the literature above, it appears many existing real-world studies imitate features of trial design. Doing so may imply a certain level of rigour but risks undermining the generalisability, validity and reliability of the results (Dziadkowiec, Durbin, Muralidharan, Novak, & Cornett, 2020). Some selection criteria are understandable such as the requirement for eyes to be treatment naïve but many real-world studies excluded eyes for reasons frequently used in trials such as co-existent age-related macular degeneration (AMD), diabetic retinopathy (DR), media opacity, retinal ischaemia or surgery in recent months (Brynskov et al., 2014; Buyru Özkurt et al., 2018; Hasegawa, Takahashi, et al., 2019; Miwa et al., 2017; Osaka et al., 2018; Ozkaya et al., 2018; Shiono et al., 2018; Son et al., 2017; J. K. Wang et al., 2016), they applied limits on acceptable baseline VA, CST or disease duration (Brynskov et al., 2014; Buyru Özkurt et al., 2018; Callizo et al., 2019; Eleftheriadou et al., 2019; Miwa et al., 2017; Osaka et al., 2018; Ozkaya et al., 2018; Shiono et al., 2018; Son et al., 2017; J. K. Wang et al., 2016; Winterhalter et al., 2018) or they implied patients were managed according to a trial-like protocol even though they were retrospective studies (Buyru Özkurt et al., 2018; de Salles & Epstein, 2021; Eleftheriadou et al., 2019; Hasegawa, Takahashi, et al., 2019; Miwa et al., 2017; Osaka et al., 2018; Ozkaya et al., 2018; Shiono et al., 2018; Son et al., 2017; J. K. Wang et al., 2016; Wecker et al., 2017). The LUMINOUS study was an exception (Lotery et al., 2022; Pearce et al., 2020), being prospective with few selection criteria but appeared to enrol fewer than one patient with RVO per centre and many patients appeared to be grossly under treated even for real-world practice.

The most frequent limitation of RW studies has been high rates of loss to follow-up – a form of selection bias (Howe, Cole, Lau, Napravnik, & Eron, 2016). A certain amount of follow-up has frequently been required for inclusion either before and/or after treatment began (I. Chatziralli et al., 2018; Jumper et al., 2018; Kiss et al., 2020; Nghiem-Buffet et al., 2017; Spooner et al., 2019; Wu et al., 2022). Some reports have been of “completers-only” without any mention of the eyes that did not complete the required follow-up (I. Chatziralli et al., 2018; Farinha et al., 2015; Spooner et al., 2019; Wu et al., 2022). One can imagine the utility of an oncology study that reports 100% 5-year survival rates in patients with 5 years of follow-up. The same applies to “completers-only” reports in retinal disease. Outcomes may be skewed by not accounting for the patients that abandoned treatment with poor outcomes or perhaps had disease resolution.

Very little evidence exists that is specific to HRVO. Eyes with HRVO have been included in either BRVO or CRVO cohorts of real-world studies as they have been in clinical trials. It remains unclear if HRVO should be regarded a variant of either BRVO or CRVO, or should be considered a separate condition (Hayreh, Zimmerman, McCarthy, & Podhajsky, 2001). Clinical trials usually documented inclusion or exclusion of HRVO, though the proportions are not always reported (Campochiaro et al., 2015). Rarely in RWE is the inclusion of eyes with HRVO either documented or quantified (Brynskov et al., 2014; Ivanovska Adjievska et al., 2017; Miwa et al., 2017).

2.4.4 Mining Data from EMR servers

Studies that mine data from electronic medical records systems tend to suffer from missing information, inconsistencies in coding and a lack of comprehensive follow-up (Getzen, Ungar, Mowery, Jiang, & Long, 2023). For example, a report using data from the US Retina database could not identify baseline visual acuity in 13025 of 30106 (35%) eyes commencing VEGF inhibitors for nAMD (Kiss et al., 2020). At first glance these studies

appear to report the treatment patterns and clinical outcomes in enormous numbers of patients, but there is no escaping selection bias when measurements are only available in a fraction of eyes.

The Vestrum Health Retina database is another group that have reported real-world outcomes using VEGF inhibitors for AMD, DMO and more recently RVO (T. Ciulla et al., 2021) The methodology, as discussed above, includes a large number of records from which a fraction were actually analysed based on follow-up or availability of measurements. For example, their DMO study included 15,608 eyes however 12-month outcomes were available in 5,840 (37%) for analysis (T. A. Ciulla, Bracha, Pollack, & Williams, 2018).

American Academy of Ophthalmology IRIS® (Intelligent Research in Sight) Registry contains extracted data regarding eyes with branch or central RVO and macular oedema (ME) treated with VEGF inhibitors in the US (Parke, Lum, & Rich, 2017; Rich, Chiang, Lum, Hancock, & Parke, 2018). Systems integrator software automatically transfers encrypted data retrieved from EMR servers of over 15,000 ophthalmologists that avoid Merit-Based Incentive Payment System (MIPS) penalties through participation (AAO, 2025; De Fauw et al., 2016). It is questionable whether IRIS should be called a registry without a pre-defined outcomes dataset. The system is enormous, including data on nearly a quarter of the US population spanning over 10 years, but analyses focus only on the demographic characteristics of patients with RVO rather than outcomes of treatment (Haller et al., 2024; Li et al., 2022).

2.4.5 Patient Registries in Observational Research

Patient registries are organised systems that use observational study methods to collect uniform data in a naturalistic way (Gliklich, 2020). Registries usually limit collection of parameters to those normally used by clinicians. Having those measurements complete and within range, stored within data fields of a minimum outcomes dataset from the start offers

obvious advantages over processes based on finding measurements within an entire electronic medical record.

Data from registries can quantify patient demographics, track the progress of disease, variations in treatment patterns, identify factors predictive of outcome, highlight quality and disparities of care delivery, alert users of safety signals through active surveillance and feedback, facilitate peer review of performance, contribute to the development of treatment guidelines, guide future research through hypothesis generation and identification of knowledge gaps, enlighten payers regarding budgeting and contribute to the fulfillment of post-marketing surveillance amongst other functions (Gliklich, 2020). The Australian Government has a particular interest in Clinical Quality Registries (CQRs) proposing six pillars for improvement including increased focus on patient-centred health care; clinical practice care and patient outcomes; quality, efficiency and cost effectiveness; transparency and access, and data linkage, integration and interoperability (Government, 2024).

The Fight Retinal Blindness! registry is an example of a CQR that has made many meaningful contributions to real-world evidence supporting the management of retinal disease using intravitreal injections (https://savesightregistries.org/research-outputs/). For example, FRB! data from patients with nAMD and DMO has been used to compare the efficacy of ranibizumab with aflibercept in routine care in separate 3-year analyses (Bhandari et al., 2020; Gabrielle et al., 2022). The 36-month nAMD analysis (N=965) found each drug similar in terms of the median injections (18), visits (21) and VA outcomes at 3 years (Crude [95% CI]: ranibizumab +1.5 letters [0 to 3.1] and aflibercept +1.6 letters [-0.2 to 3.3]; P = 0.97, and after adjustment [95% CI]: ranibizumab +0.3 letters [-1.5 to 2.0] and aflibercept +1.0 letters [-0.7 to 2.8]; P = 0.66). The 36-month DMO analysis (N=534) found each drug effective however there was a small but significant difference in VA outcomes at 3 years, favoring aflibercept (After adjustment [95% CI]: ranibizumab +1.3 letter [-0.1 to 4.2] and aflibercept +2.4 letters [-0.2 to 5.1]; P = 0.001) and CST improvements, also favoring

aflibercept (After adjustment [95% CI]: ranibizumab -87.8 [-108.3 to -67.4] μm and aflibercept -114.4 [-134.4 to -94.3]; $P < 0.01$) including earlier resolution of DMO with aflibercept.

A spectrum exists within trial design that spans from the traditional (explanatory) RCTs to trials that are more reflective of real-world practice known as pragmatic clinical trials (PCTs). The degree of pragmatism can be graded by nine PRECIS-2 (PRagmatic Explanatory Continuum Indicator Summary) domains, many of which align with the principles adhered to when reporting quality real-world evidence using FRB! data. These domains have been adapted from Loudon et al in table 2.1 (Loudon et al., 2015). There are of course obvious differences between FRB! studies and trials including the non-random allocation of treatment and the retrospective nature of analyses when using registry data. Nevertheless, like PCTs, analyses using FRB! data have broad eligibility, patients are recruited in a naturalistic way, care is delivered in typical settings by typical doctors, outcomes reflect the flexibility of care delivery and treatment adherence in routine practice that is relevant to all participants.

Table 2.1. The nine PRECIS-2 domains for assessment of the pragmatism of trials. [#]

Domain	Assessment of pragmatism
Eligibility	To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
Organisation	How different are the resources, provider expertise, and the organisation of care delivery in the intervention arm of the trial from those available in usual care?
Flexibility (delivery)	How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?
Flexibility (adherence)	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
Follow-up	How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?
Primary outcome	To what extent is the trial's primary outcome directly relevant to participants?

Primary analysis	To what extent are all data included in the analysis of the primary outcome?
# Information in this table adapted from Loudan et al (Loudon et al., 2015)	

2.4.6 Research Objectives

After reviewing the trials and real-world studies, most retinal specialists would still struggle to answer simple questions from patients with RVO commencing VEGF inhibitors in routine practice.

"How many injections am I likely to need? Which of the approved drugs will give me the best outcomes, aflibercept or ranibizumab? I am going back home to New Zealand, will bevacizumab suffice? I understand that treatment will get this under control, but does this go on forever, is there a chance I can stop getting needles? What are my chances of having driving vision or being blind in that eye years from now? What does it mean when you say that studies do not include patients like me because I have HRVO, or my vision is too good or too bad?"

The primary objectives of this thesis are to provide answers to these questions and to offer more robust evidence to inform management decisions in routine care using VEGF inhibitors for RVO. Many of the gaps in knowledge relate to the limitations of both clinical trial and existing real-world evidence reviewed above. Trials tend to have short duration (typically 12-24 months) and report outcomes in highly select cohorts treated very frequently. RWE tends to suffer from poor quality data and frequently reports outcomes only in eyes completing a certain period of follow-up.

The next chapter will outline the methods used to collect and store a large, high-quality real-world outcomes dataset within the prospectively designed RVO module of the FRB! registry. This will include a description of statistical methods tailored to analyse these data, providing

prognostic information applicable to all patients initiating VEGF therapy for RVO in routine care.

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CHAPTER 3: METHODS.

3.1 The Fight Retinal Blindness! registry

The prospectively designed web-based Fight Retinal Blindness! (FRB) registries track the real-world treatment outcomes of various macular diseases including nAMD, DME and retinal vein occlusion (Gillies et al., 2014). The levels of functionality in the registry include a clear graphical representation of the “treatment journey” for individual patients, a system of audit for individual doctors that is benchmarked against peers and a large repository of anonymised high-quality data for international, multicentre, observational research projects. The parameters collected at each patient visit in FRB! constitute a prospectively defined, minimum outcomes dataset which is limited to those of greatest relevance to clinical management. Quality assurance mechanisms ensure accuracy as well as completeness of the data. Visits are finalised only when all parameters are complete and within prespecified range.

Systems that support the FRB! project prioritise robust data quality, anonymity and security. No additional information is stored beyond what is described below. Anonymised data are encrypted for transmission and storage at the University of Sydney’s Information and Communication Technology Department. All proposed studies require approval through the FRB! project publications committee after which a statistical analysis plan is required adhering to the tenets of the declaration of Helsinki. Ethics and data protection approval for the FRB! project has been granted in Australia, New Zealand and Switzerland, through the Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09), the Southeastern Sydney Local Health District Human Research Ethics Committee and the Cantonal Ethics Commission in Zurich (PB_2016-00264). Local Institutional Review Board (IRB) approval has been granted for participation in the FRB! project in 17 other participating countries.

3.2 The FRB! RVO Module

FRB! designed the retinal vein occlusion module in 2011 to monitor and track treatment outcomes of patients with MO due to RVO. Figure 3.1 demonstrates the simplicity of the user interface along with the graphical representation of progress including plots of VA, CST, treatments delivered and oedema activity over time.

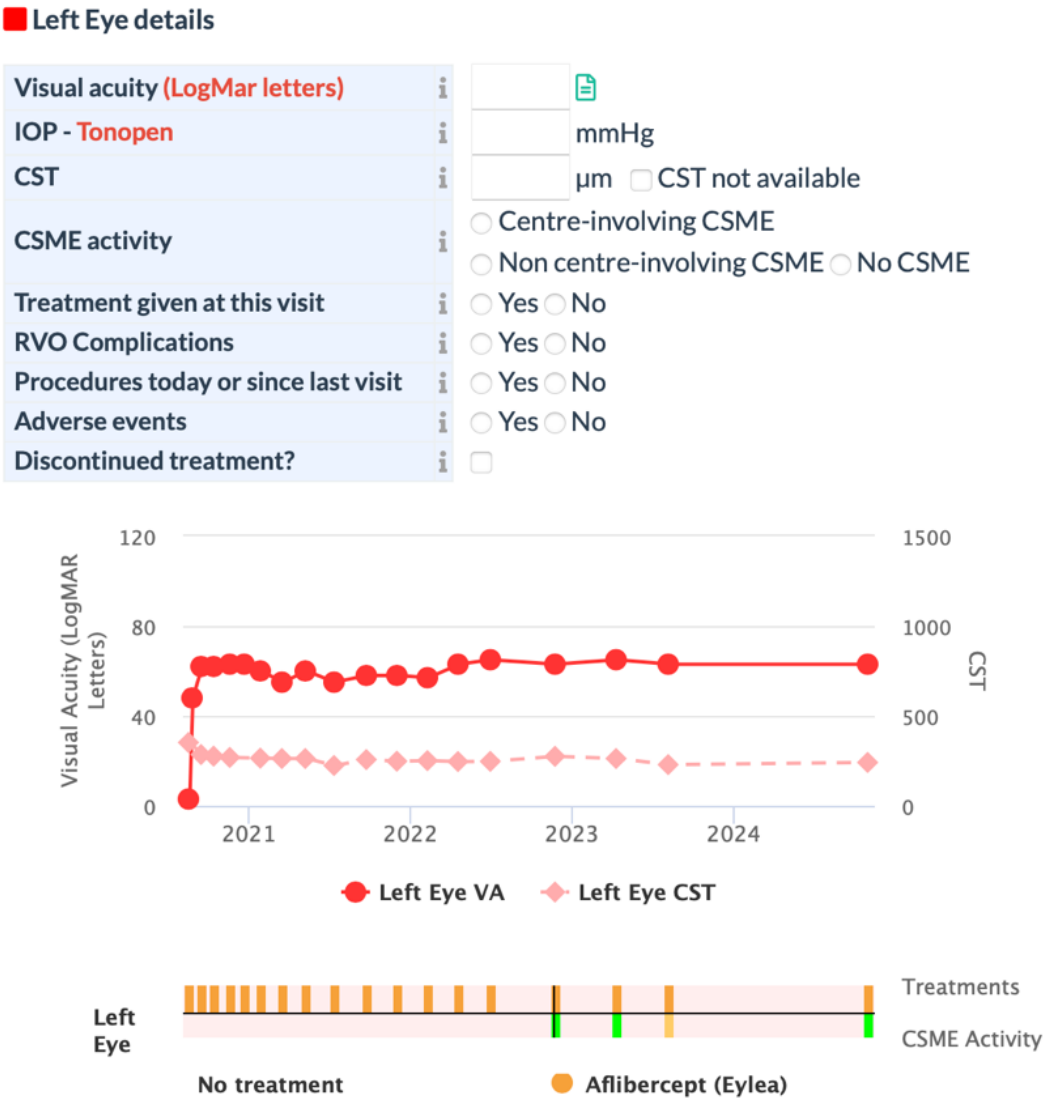
New patients added to the FRB! registry are assigned a unique identifier at the first, or baseline, visit, which is generally when the first treatment is given. Dropdown menus facilitate selection of the appropriate audit (RVO, nAMD, DMO, etc), the primary clinician, a secondary clinician (if required), ethnicity, gender (Male, Female, Undisclosed), year of birth, postcode and smoking status (Smoker, Non-Smoker, Ex-Smoker, Unknown/Undisclosed). Additional baseline characteristics in the RVO module include RVO subtype (BRVO, CRVO, HRVO), co-existent ocular conditions, details of pretreatment, ischaemic angiography findings, hypertension, diabetes (type 1, type 2) and presence of glaucoma (Table 3.1).

Visual acuity is entered as the most letters read on a Logarithm of minimum angle of resolution (Log MAR) acuity chart (best of unaided, aided or pinhole), intraocular pressure, central subfield thickness (CST, in microns), the presence or absence of clinically significant macular oedema (CSME: Centre-involving, Non-centre-involving, No CSME) as judged by the treating physician, treatments given at that visit, RVO complications, procedures that day or since the last visit, adverse events and discontinuation of treatment reasons when necessary with additional drop-down menus (Table 3.1).

Table 3.1 Extended listing of possible selections from dropdown menus in the RVO module of the FRB! registry.

Ethnicity: White/Caucasian, Black/African, Asian, Polynesian Melanesian, Pacific islander, Australian Aboriginal/Torres Strait Islander, American Indian or Alaskan native, Māori, Hispanic, Fijian Indian, Indian, Middle eastern, Mixed, Unable to specify.
Co-existent ocular conditions: none, amblyopia, foveal atrophy, axial myopia, media opacity, DR, nAMD, optic neuropathy including glaucoma, posterior uveitis, pseudophakia, vitreomacular traction or fibrosis.
Details of pretreatment: none, aflibercept, bevacizumab, ranibizumab, brolucizumab, triamcinolone, dexamethasone implant, faricimab, fluocinolone implant, macular laser, prp/sectoral laser, vitrectomy.
Ischaemic angiography findings: FFA not performed, No Ischaemia, Macular ischaemia, Peripheral Ischaemia.
Treatments given at this visit: aflibercept 2mg (Eylea 2mg), bevacizumab (Avastin), aflibercept 8mg (Eylea 8mg), bevacizumab (Mvasi), brolucizumab (Beovu), faricimab (Vabysmo), ranibizumab (Lucentis), fluocinolone implant (Iluvien), brolucizumab (Vsiqq), ranibizumab (Ranivisio), ziv-aflibercept (Zaltrap), ranibizumab (Ximluci), laser-induced chorioretinal anastomosis, laser prp / sectoral prp, macular laser, macular surgery, dexamethasone implant (Ozurdex), sub-threshold laser, triamcinolone, vitrectomy.
RVO Complications: Neovascularization of the disc – NVD, Neovascularization elsewhere – NVE, Vitreous haemorrhage, Neovascularisation of iris/angle – NVI/A, Rubeotic glaucoma, Macular changes affecting vision (Epiretinal membrane [ERM], macular hole, pigment clumping, atrophy), Elevated IOP requiring change in therapy.
Procedures today or since last visit: none, cataract extraction, macular surgery, YAG-capsulotomy, vitrectomy, laser trabeculoplasty, incisional glaucoma surgery.
Adverse Events: none, retinal detachment, non-infectious endophthalmitis, infectious endophthalmitis, vitreous haemorrhage from injection, traumatic cataract, anterior uveitis, vitritis, non-occlusive retinal vasculitis, occlusive retinal vasculitis, chorioretinitis.
Reason for discontinued treatment: evisceration or enucleation, treatment successful, further treatment futile, patient goes to another doctor, patient declines, medically contraindicated, deceased.

Figure 3.1. Web-based graphical user interface for entry of visit data including plots of preceding observations. Treatment using aflibercept for MO due to left CRVO in this example commenced in August 2021 (red circles = visual acuity and faint red diamonds = CST). Below the plot are bars indicating previous treatments and disease activity (Intravitreal treatment bars: green = bevacizumab, purple = ranibizumab, yellow/brown = aflibercept, blue = dexamethasone implant and white = no treatment. CSME bars: red = centre-involving CSME, yellow = non-centre involving CSME and green = no CSME).



3.3 Statistical analysis

Specific statistical methods are required when analysing real-world data. It is necessary to manage both the irregularity of visits without a protocol and the non-random allocation of different treatments delivered to patients in routine care.

Few patients will have a convenient visit occurring at the study conclusion (e.g. 12-month outcomes). Some extrapolation from the closest visit is necessary (e.g. 365 days +/- 60 days). It is important not to overuse last observation carried forward or back, but with a smaller window more eyes will be declared non-completers even if they have visits afterwards.

There are no convenient outcomes in real-world data occurring at regular intervals for simple description or plotting as there may be in trials. To address this, locally estimated scatterplot smoothing (LOESS) can combine asynchronous observations by fitting a function that describes overall trends using least squares and non-linear regression (Cleveland, 1979). LOESS is also effective in dealing with outliers in the data, placing greater weight on data closer to the function being built. There are, however, potential limitations with LOESS; it is best considered “descriptive” and has no capacity for adjustment for covariates as it assumes a simple relationship exists between the dependant and independent variables of interest (bivariate).

The non-random allocation of treatment in routine care can produce groups that differ significantly making it more appealing to use models that can account for covariates (Cox, 2006). For example, doctors in routine care may reserve one treatment for eyes with more severe disease. In this instance, LOESS may well “describe” outcomes but, a multivariate model would better “compare” the treatments by adjusting outcomes for differences in baseline VA, CST and age between groups. There is also potential for adjustment for “nesting” when eyes in a study are from the same patient or from different patients but managed by the same practitioner.

Poisson generalised additive mixed effects models (GAMMs) are particularly suited to the analysis of real-world data (Zuur, Saveliev, & Ieno, 2014). GAMMs address the asynchronous timing of visits, they incorporate adjustments for fixed effects (e.g. age,

baseline VA or CST) and random effects (e.g. nesting within patients or practices) and produce predictions of outcomes based on observations from all eyes commencing therapy, rather than just completers.

Depending on the analysis, all eyes can contribute observations to the models up until they complete the study, they switch treatment or non-complete. Observations are generally censored from the models after eyes switch from their original VEGF inhibitor (when comparing one VEGF inhibitor with another) or possibly only if they switch to steroids (when predicting outcomes with VEGF inhibitors combined). The models assume the trajectory of switchers and non-completers would have likely followed that of similar eyes that completed the study had they not switched or been lost to follow-up. For our purposes, these models provide mean adjusted VA and CST predictions along with 95% confidence intervals facilitating robust comparison of outcomes by group from commencement of treatment until the end of the study period.

Kaplan-Meier (KM) curves visually represent the probability of an event occurring over time where not all subjects are followed until the event occurs (Rich et al., 2010). Subjects will either have the event occur or not occur, some may be lost to follow-up before or after the event occurs and in some the event may occur after the study period has concluded. The size of the stepwise progression in the KM curve when an event occurs is made proportional to the number of subjects still at risk, participating in the study at that time. This accounts for erosion of cohorts through loss to follow-up and the prior occurrence of the event in some subjects. For example, in 20 patients with RVO we may be interested in comparing “if and when” 10 eyes treated with one drug achieved inactivity of macular oedema compared with 10 eyes treated with another drug during a 12-month study. If at a point in the study one member of each group has the event occur but at the same time 4 subjects from one group are lost to follow-up then the chances of a subsequent event differ in the groups because it could next happen in 1 of 9 subjects in one group but in 1 of only 5 subjects in the other

group. The size of the next step in the KM curve reflects the proportion of the remaining cohort. In this instance another patient having the event in each group would deflect the curve by 1/9 in one group but by 1/5 in the other.

Cox proportional hazards models enable adjusted comparison of data used to generate KM curves. This is useful in observational research when treatment is non-randomly allocated resulting in differences between groups at baseline (fixed and random effects) (Cox, 1972). Similar mixed effects (fixed and random) modelling techniques can be applied to compare count data (e.g. injections or visits) that account for differences at baseline in groups and in rates of loss to follow-up associated with the intervention each group receives. This technique of comparing count data incorporates the count data in all eyes, including data up until non-completion or switching, rather than data just in completers.

The statistical analyses in this project were performed using R statistical software (https://www.r-project.org/) integrated with RStudio (https://www.rstudio.com/). These open-source programmes work together and are supported by a strong statistical community that regularly write and update packages extending the functionality of the base code and allowing application of the latest techniques to the manipulation of large datasets. Fluency in the programming language of R is necessary to write scripts for analyses. The time and effort I took in learning the language and developing scripts was worthwhile as it made analyses reproducible unlike programmes that rely on a graphical user interface. Packages suited to this project included *glmmTMB* (1.0.1), *itsadug* (V2.4) and *mgcv* (V1.8-31) for generalised linear or generalised additive mixed effects models, *survival* (3.1-12) for Kaplan-Meier estimates and *coxme* (2.2-16) for Cox mixed effects models (R Core Team, 2020).

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CHAPTER 4: 12-MONTH OUTCOMES OF RANIBIZUMAB VERSUS AFLIBERCEPT FOR MACULAR OEDEMA IN CENTRAL RETINAL VEIN OCCLUSION: DATA FROM THE FRB! REGISTRY.

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4.1 Abstract

Purpose: To compare 12-month treatment outcomes of eyes receiving aflibercept or ranibizumab for macular oedema secondary to central retinal vein occlusion (CRVO) in routine clinical practice.

Methods: 296 treatment-naïve eyes receiving either aflibercept (171 eyes, 2mg) or ranibizumab (125 eyes, 0.5mg) for macular oedema secondary to CRVO were recruited retrospectively from centres using the prospectively designed FRB! registry. The primary outcome measure was the mean change in LogMAR letter scores of visual acuity (VA). Secondary outcomes included change in central subfield thickness (CST), injections and visits, time to first grading of inactivity, switching and non-completion from baseline to 12 months.

Results: Baseline VA (SD) was somewhat better in aflibercept vs. ranibizumab treated eyes (42.5 ± 25.5 letters vs. 36.9 ± 26 letters; P = 0.07) with similar CST (614 (240) µm vs. 616 (234) µm: P = 0.95). The 12-month adjusted mean (95%CI) VA change was +16.6 (12.9, 20.4) letters for aflibercept vs. +9.8 (5.5, 14.1) letters for ranibizumab (P = 0.001). The mean (95%CI) adjusted change in CST was significantly greater in aflibercept vs ranibizumab treated eyes: -304 (-276, -333) μm vs. -252 (-220, -282) μm, (P < 0.001). Both groups had a median (Q1, Q3) of 7 (5, 9) injections and 10 (8,13) visits. Aflibercept-treated eyes became inactive sooner than ranibizumab (P = 0.02). Switching occurred more commonly from ranibizumab (26 eyes, 21%) than from aflibercept (9 eyes, 5%) (P < 0.001).

Conclusion: Both aflibercept and ranibizumab improved VA and reduced CST in eyes with CRVO in routine clinical practice, with aflibercept showing significantly greater improvements in this comparative analysis.

4.2 Introduction

Treatment of central retinal vein occlusion (CRVO) has progressed from prevention of sight-threatening sequelae(Hayreh, 2003) to vascular endothelial growth factor (VEGF) inhibitors, which randomised controlled trials (RCTs) suggest can improved vision significantly (Boyer et al., 2012; Brown et al., 2013a; Campochiaro et al., 2011; Korobelnik et al., 2014a). There are, however, limited data showing that these impressive RCT outcomes are being achieved in routine clinical care and whether the licensed drugs, aflibercept and ranibizumab, are equivalent in the general population.

RCTs mandate frequent intravitreal injections that pose a significant treatment burden which is difficult to always achieve in routine clinical practice (Kiss et al., 2014; Lotery & Regnier, 2015; Stallworth, Akshay, Constantine, Stinnett, & Fekrat, 2020). Various retrospective observational analyses suggest that fewer injections are given in the first 12 months than in RCTs, with correspondingly lower visual acuity gains (Callizo et al., 2019; Chatziralli et al., 2018; Chatziralli, Theodossiadis, Moschos, Mitropoulos, & Theodossiadis, 2017; Kitagawa et al., 2018). On average 4 to 5 injections were given in the first 12 months, resulting in an average visual gain of approximately 1.2 lines (Gale et al., 2020; Lotery & Regnier, 2015; Stallworth et al., 2020).

The LEAVO study was a randomised clinical trial that reported that ranibizumab was non-inferior to aflibercept in CRVO (Hykin et al., 2019). There were selected cohorts treated under controlled conditions following a strict induction protocol followed by a PRN regimen from week 16 to week 96, which may be similar to routine clinical care. The VA outcomes at 12 months were similar between aflibercept- and ranibizumab-treated eyes (Hykin et al., 2019). The SCORE2 study reported the non-inferiority of bevacizumab compared to aflibercept in a heterogeneous group of eyes with CRVO or HRVO (Scott et al., 2017).

The quality of data from routine clinical practice is variable. “Mining” large datasets from electronic medical records currently produces lower quality data, such as a recent report using data from the US Retina database, where baseline visual acuity could not be identified in 13025 of 30106 (35%) of eyes receiving anti-VEGF treatment for age-related macular degeneration (Kiss et al., 2020). Outcomes registries with pre-specified mandatory fields - such as the Fight Retinal Blindness! Project – require users to enter all data within pre-specified ranges for the visit to be “finalised” and accepted into the database. Finalisation rates consistently exceed 95% of recorded visits. The additional effort users make produces higher quality, complete datasets.

Here we report a comparative analysis of 12-month treatment outcomes of a large cohort of patients in routine clinical practice who received aflibercept or ranibizumab for macular oedema secondary to CRVO from participating centres in the Fight Retinal Blindness! Project.

4.3 Materials And Methods

4.3.1 Design and setting

We conducted a retrospective analysis of eyes with CRVO treated with approved intravitreal anti-VEGF agents. Treatment was tracked in routine clinical practice within the prospectively designed retinal vein occlusion module of the Fight Retinal Blindness! Registry.(Gillies et al., 2014) Participants were treatment-naïve and managed at clinics in Australia, France, Switzerland and the United Kingdom. Ethics and data protection approval was obtained from the University of Sydney and the Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09), the French Institutional Review Board (2017_CLER-IRB_II-05), the Cantonal Ethics Commission in Zurich (PB_2016-00264), and the Caldicott Guardian of the Royal Free London NHS Foundation Trust (Dr Kilian Hynes). The study

adhered to the STROBE checklists for reporting observational studies(von Elm et al., 2008) and followed the tenets of the Declaration of Helsinki. All patients gave informed consent. An “opt-in” informed consent was sought from patients from France, Switzerland and the United Kingdom. An “opt-out” patient consent was approved by ethics committees in Australia.

4.3.2 Data Sources and Measurements

Data were collected at each clinical visit including the number of letters read on a logarithm of the minimum angle of resolution (log MAR) VA Chart (highest of uncorrected, corrected or pinhole), the activity (presence of intraretinal cystoid changes) of cystoid macular oedema (CME [yes / no]), the central subfield thickness (CST [μm]) measured using spectral-domain optical coherence tomography (OCT), treatment given, other ocular procedures and ocular adverse events. Relevant systemic risk factors or ocular conditions were recorded at baseline only, as was the type of RVO (CRVO, hemi-RVO or branch-RVO),(McAllister, Tan, Smithies, & Wong, 2014) and if a fluorescein angiogram was performed, whether macular or peripheral ischaemia was documented. Drug choice and treatment frequency were at the physician’s discretion in consultation with the patient reflecting routine clinical practice.

4.3.3 Patient selection

Treatment-naïve eyes that started treatment with either ranibizumab (0.5mg Lucentis, Genentech Inc/Novartis) or aflibercept (2mg Eylea, Bayer) from 1 June 2014 to 1 June 2019 were studied. Eyes with hemi-RVO or branch-RVO were excluded. Eyes that had at least three visits and were followed for 12 months were defined as “completers”. Switchers were defined as eyes that received ≥2 injections of the other drug prior to switching. Visits occurring after the switch were not included in this analysis. Eyes that did not complete 12 months of observations were defined as “non-completers”.

4.3.4 Outcomes

The main outcome was the mean change in VA at 12 months between anti-VEGF agents. Secondary outcomes were the mean change in CST, number of visits and the number of injections. Other event-based outcomes of interest were first grading of CME inactivity, switching and non-completion rates over 12 months.

4.3.5 Statistical analysis

Descriptive data were summarised using the mean, standard deviation, median, first and third quartiles, and percentages where appropriate. Eyes were observed from the first treatment visit to their 12-month (365 ± 30 days) visit. T-tests, Wilcoxon signed-rank tests, Chi-square tests and Fisher's exact tests were used as appropriate to compare baseline characteristics between ranibizumab and aflibercept treated eyes. Calculation of crude visual and anatomic outcomes at 12 months used the last-observation-carried-forward (LOCF) for switchers and non-completers. We used longitudinal generalised additive mixed-effects models to compare VA and CST outcomes between the treatments over the 12-month period with the interaction between injection group and time as the main predictor. The longitudinal models included all visits up until 12 months from completers, non-completers and switchers without imputation of missing data (i.e. LOCF). Visits occurring after an eye switched drugs were not included. We adjusted for age and baseline VA or CST as fixed effects, and nesting of outcomes within doctor and patient (for bilateral cases) as random effects. We used predictions from these models to plot predicted VA and CST, and the difference in the mean predicted VA and CST, over 12 months for each drug.

Generalised Poisson linear mixed models were used to compare visits and injections with an offset for log days of follow-up. Kaplan-Meier survival analysis was used to assess the time to first grading of CMO inactivity, non-completion and switching. A Cox-proportional hazards model was used to compare time to inactivity between treatment groups. Generalised

Poisson and Cox-proportional hazards models were adjusted for age, baseline VA and baseline CST as fixed effects, and nesting of outcomes within doctor and patient as random effects.

All analyses were conducted using R version 4.0.0 (http://www.R-project.org/) using the *glmmTMB* (V1.0.1) package for generalised linear mixed-effects regression, the *mgcv* (V1.8-31) package for generalised additive mixed models, and the *coxme* (V2.2-16) and *survival* (V3.1-12) packages for time-to-event analyses (Magnusson, 2020; R Core Team, 2020; T. Therneau, 2020; T. M. Therneau, 2020; Wood, 2019).

4.4 Results

4.4.1 Study participants

We identified 296 treatment-naïve patient eyes (125 ranibizumab and 171 aflibercept) in 291 patients with cystoid macular oedema secondary to CRVO that started treatment with either ranibizumab or aflibercept from June 1, 2014, and June 1, 2019 (Table 4.1).

There were no statistically significant differences at baseline in eyes grouped by VEGF inhibitor. Eyes receiving ranibizumab were slightly older (73 vs. 71 years; P = 0.14), had lower mean baseline visual acuity (36.9 vs. 42.5 letters; P = 0.07), more presented with VA ≤ 35 letters (45% vs. 38%, P = 0.29) and were less likely to have a history of systemic hypertension and glaucoma than those receiving aflibercept. The groups had very similar mean (SD) baseline CST (ranibizumab 614 (240) µm vs. aflibercept 616 (234) µm; P = 0.95). FFA was performed in 60% of all eyes studied. Twenty eyes overall that had documented macular ischaemia were more likely to have baseline visual acuity ≤ 35 letters (P = 0.01); however, the treatment groups had no significant difference in documented ischaemia at baseline including both macular (7%) and peripheral ischaemia (25%).

Table 4.1. Demographic Characteristics of all treatment-naïve CRVO eyes commencing ranibizumab or aflibercept treatment 2014 – 2019.

	Overall	Ranibizumab	Aflibercept	P-value
Eyes, n	296	125	171	
Patients, n	291	122	170	
Female, %	47%	47%	47%	1.00
Age, mean (SD)	72 (13)	73 (12)	71 (13)	0.14
VA, mean (SD)	40.1 (25.8)	36.9 (26)	42.5 (25.5)	0.07
≥ 70 letters, %	13%	13%	13%	1.00
≤ 35 letters, %	41%	45%	38%	0.29
FFA Performed, n (%)*	176 (59%)	75 (60%)	101 (59%)	0.96
Macular Ischaemia, n (%)	20 (7%)	9 (7%)	11 (6%)	0.81
Peripheral Ischaemia, n (%)	75 (25%)	37 (30%)	38 (22%)	0.16
CST, mean (SD)	615 (236)	614 (240)	616 (234)	0.96
Hypertension, %	60%	58%	61%	0.80
Glaucoma, %	16%	14%	17%	0.53
Country, %				
Australia	29%	30%	29%	
France	31%	39%	25%	
Switzerland	24%	15%	32%	
United Kingdom	15%	16%	15%	

n = Number, SD = Standard Deviation, VA = Visual Acuity (log MAR letters), FFA = Fundus Fluorescein Angiography, CST = Central Subfield Thickness (in microns). *Not mandatorily performed or documented.

4.4.2 Visual outcomes at 12 months

Mean crude VA improvement (95% confidence interval [CI]) was higher for aflibercept than for ranibizumab (+13.1 letters [9.4, 16.8] vs. +9.9 [5.8, 14.1] (P = 0.26), including eyes that switched or dropped out (using LOCF) (Table 4.2).

This trend was more pronounced in eyes presenting with baseline VA ≤ 35 letters (38% in the aflibercept treated group and 45% in the ranibizumab treated group) with mean crude VA improvement in the aflibercept group of +24.6 (18.5, 30.7) letters vs. +16.6 (10.4, 22.8) letters in the ranibizumab group (P = 0.07) from similar mean baseline VA: 13.7 (13.7) letters vs. 11.9 (13.2) letters (P = 0.46) (Table 4.3). The treatment groups started with very similar proportions of eyes with VA ≥ 70 at baseline (13%); however, more eyes in the aflibercept

group (42%) had VA ≥ 70 letters at 12 months than in the ranibizumab group (30%; P = 0.05).

Table 4.2. 12-month outcomes in all eyes and stratified by anti-VEGF agent received. Significant P-values comparing ranibizumab and aflibercept are highlighted in bold.

	Overall	Ranibizumab	Aflibercept	P-value
No of Eyes	296	125	171	
Baseline VA, mean (SD)	40.1 (25.8)	36.9 (26)	42.5 (25.5)	0.07
Final VA, mean (SD)	51.9 (28.5)	46.9 (29.4)	55.5 (27.3)	0.01
Crude VA change, mean (95% CI)	11.8 (9, 14.5)	9.9 (5.8, 14.1)	13.1 (9.4, 16.8)	0.26
Adjusted VA change, mean (95% CI) [α]		9.8 (5.5, 14.1)	16.6 (12.9, 20.4)	0.001
Gained ≥ 15 letters (%)	46%	40%	50%	0.10
Lost ≥ 15 letters (%)	10%	10%	11%	0.95
VA ≥ 70 %Baseline / %Final	13% / 37%	13% / 30%	13% / 42%	1.00/0.05
VA ≤ 35 %Baseline / %Final	41% / 28%	45% / 34%	38% / 24%	0.29/0.09
CST Baseline, mean (SD)	615 (236)	614 (240)	616 (234)	0.95
CST Final, mean (SD)	336 (169)	369 (179)	314 (159)	0.01
CST Change, mean (95% CI)	-279 (-311, -247)	-245 (-292, -197)	-302 (-345, -258)	0.10
Adjusted CST Change, mean (95% CI) [α]		-252 (-220, -282)	-304 (-276, -333)	< 0.001
Completers, n (%)	236 (80%)	99 (79%)	137 (80%)	0.70
Switchers, n (%)	35 (12%)	26 (21%)	9 (5%)	< 0.001
Lost to follow up, n (%)	60 (20%)	26 (21%)	34 (20%)	
Injections, median (Q1, Q3) *	7 (5, 9)	6 (4, 9)	8 (5, 9)	0.62
Visits, median (Q1, Q3) *	10 (8, 13)	10 (7, 13)	10 (8, 13)	0.84

n – Number, VA – Visual Acuity, SD – Standard Deviation, CI – Confidence Interval, CST – Central Subfield Thickness, Q1 – First Quartile, Q3 – Third Quartile. All Eyes – Includes completers, switchers and Non-completers. "Completers" – Eyes with 12 months of observation from the start of treatment, "Switchers" – Eyes receiving ≥2 injections of the other treatment drug prior to completion of 12 months from the start of treatment. Observations were included in the analysis only up to the first occurrence of switching agents. "Non-Completers" – Eyes not completing 12 months of observations from the start of treatment. * Last observation carried forward for switchers and non-completers. [α] Calculated from longitudinal models adjusting for age and baseline VA (fixed effects), and practice and intra-patient correlation for bilateral cases (random effects).

Table 4.3. 12 Month outcomes in CRVO eyes with Baseline VA ≤ 35 Letters and VA > 35 Letters and stratified by Anti-VEGF agent received

	Baseline VA ≤ 35 Letters		Baseline VA > 35 Letters	
	Ranibizumab	Aflibercept	Ranibizumab	Aflibercept
No of Eyes	56	65	69	106
Baseline VA, mean (SD)	11.9 (13.2)	13.7 (13.7)	57.3 (12.6)	60.1 (10.6)
Final VA, mean (SD)	28.4 (27.6)	38.3 (27.5)	61.8 (21.3)	66.1 (21.2)
Crude VA change, mean (95% CI)	16.6 (10.4, 22.8)	24.6 (18.5, 30.7)	4.6 (-0.7, 9.8)	6.0 (1.8, 10.2)
Gained ≥ 15 letters (%)	45%	62%	36%	43%
Lost ≥ 15 letters (%)	2%	3%	16%	15%
VA ≥ 70 %Baseline / %Final	0% / 9%	0% / 14%	23% / 48%	21% / 59%
VA ≤ 35 %Baseline / %Final	100% / 62%	100% / 45%	0% / 10%	0% / 11%
CST Baseline, mean (SD)	693 (256)	716 (286)	563 (216)	557 (174)
CST Final, mean (SD)	388 (218)	296 (145)	357 (148)	325 (167)
CST Change, mean (95% CI)	-305 (-389, -221)	-419 (-498, -341)	-205 (-259, -151)	-232 (-278, -186)
Completers, n (%)	42 (75%)	49 (75%)	57 (83%)	88 (83%)
Switchers, n (%)	14 (25%)	3 (5%)	12 (17%)	6 (6%)
Lost to follow up, n (%)	14 (25%)	16 (25%)	12 (17%)	18 (17%)
Injections, median (Q1, Q3) *	6 (4, 9)	8 (5, 9)	7 (4, 9)	7 (5, 9)
Visits, median (Q1, Q3) *	10 (7, 14)	11 (9, 14)	10 (8, 12)	10 (8, 12)
*Injections and visits were calculated for completers only				

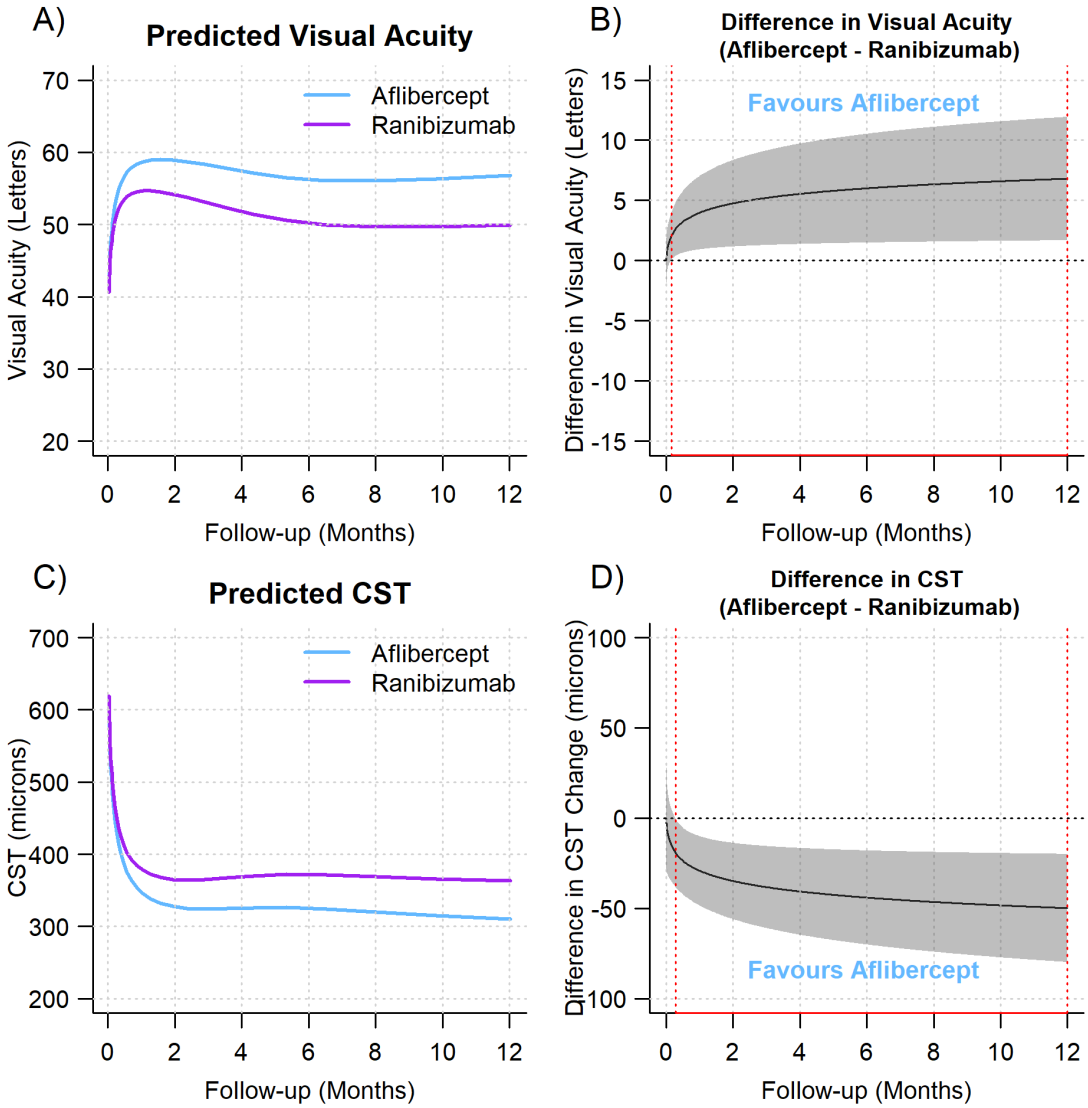
The generalised additive mixed model (*Methods*) predicted a mean adjusted VA change (95% CI) that was greater with aflibercept +16.6 (12.9, 20.4) letters than +9.8 (5.5, 14.1) letters with ranibizumab group (P = 0.001). The mean adjusted VA over 12 months for each group is shown in Figure 4.1A, while Figure 4.1B shows the difference in longitudinal trend between drugs. Eyes on aflibercept achieved larger gains in VA than ranibizumab which are statistically significant from the first week onwards to 12-months.

4.4.3 Macular thickness

Both drugs were effective in reducing macular thickness (Table 4.2). Mean baseline CST (SD) was very similar (ranibizumab 614 (240) µm vs. aflibercept 616 (234) µm; P = 0.95), however at 12 months the mean CST (SD) was significantly lower in the aflibercept group at 313 (157) µm vs. 370 (180) µm in the ranibizumab group (P = 0.01). The difference in crude

effect on CST of aflibercept compared with ranibizumab was more marked in the 121 eyes (41%) presenting with poor VA ≤ 35 letters (Table 4.3). This subset presented with similar mean CST of 716 (286) µm in the aflibercept group vs. 693 (256) µm in the ranibizumab group (P = 0.67), however the aflibercept-treated eyes had lower final CST of 296 (145) µm vs. 388 (218) µm (P = 0.03), and greater crude CST change of -419 (-498, -341) µm vs. -305 (-389, -221) µm (P = 0.08), than the ranibizumab-treated eyes at 12 months.

Figure 4.1. Graphical representation of Vision and CST by drug. Predictions from longitudinal generalised additive models of adjusted visual acuity (A and B) and CST (C and D). Red dotted lines in (B and D) indicate periods in which the confidence interval of the difference between drugs no longer crosses zero.



Application of a generalised additive mixed model predicted a greater mean adjusted CST change (95% CI) for aflibercept of -304 (-276, -333) µm vs. -252 (-220, -282) for ranibizumab ($P < 0.001$). The statistically significant longitudinal trend favouring aflibercept is shown in Figures 4C-1D extending from the first 2 weeks through 12 months.

4.4.4 Treatments and visits

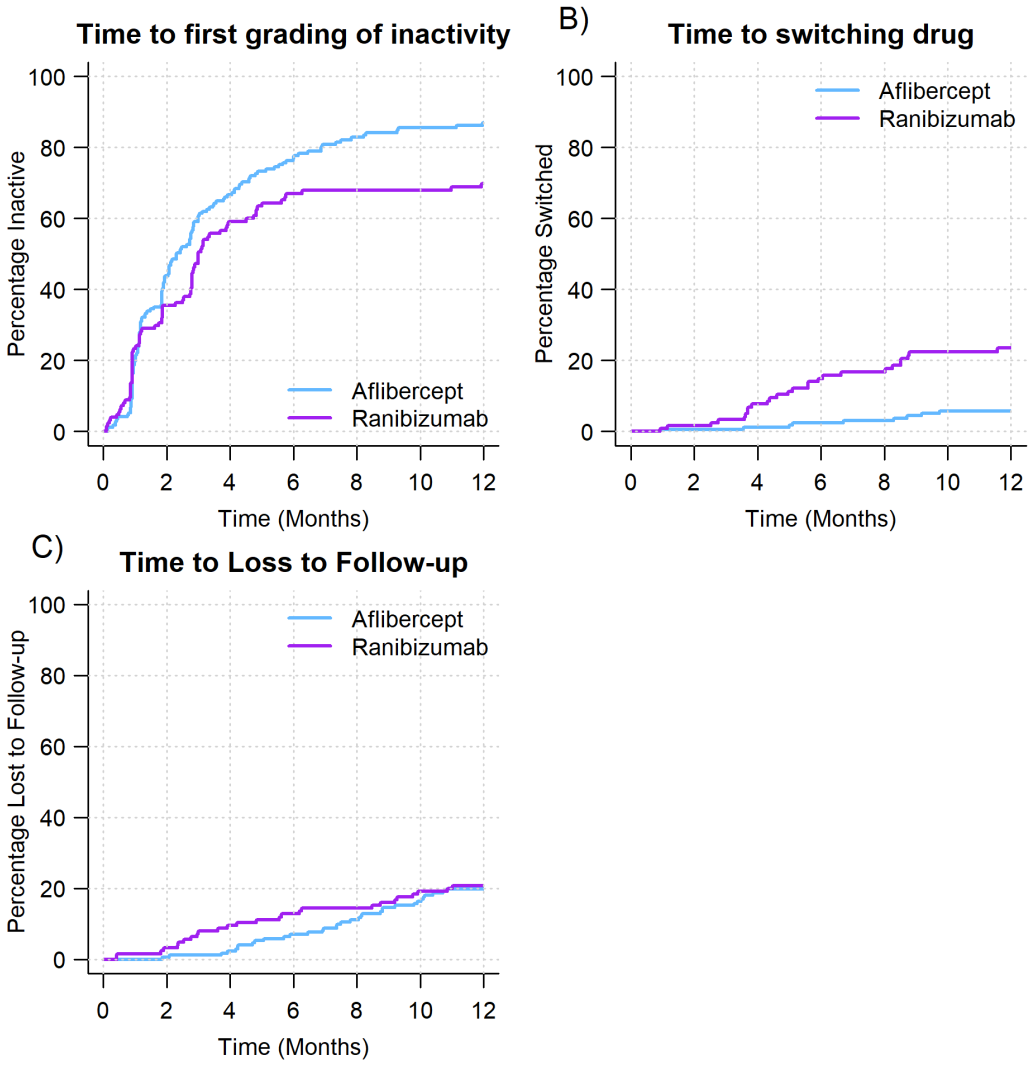
The completers (80%) in the aflibercept group had a median (Q1, Q3) of 8 (5, 9) injections, and 10 (8,13) visits, while the completers (79%) in the ranibizumab group had 6 (4, 9) injections and 10 (7,14) visits ($P = 0.62$, 0.84; Table 4.2). Thus, aflibercept treated eyes received somewhat more injections, but this difference was not statistically significant. The range in injections delivered was from 1 to 13 over 12 months. Both groups received a similar number of injections: completers had a mean total of 7.4 injections (7.5 aflibercept, 7.2 ranibizumab) over 12 months. The mean number of injections in the first six months was 4.8 (4.8 aflibercept, 4.7 ranibizumab), and 2.6 (2.7 aflibercept, 2.6 ranibizumab) in the second six months. The median time between each of the 1st to 5th injections was 4, 4, 6 and 6 weeks. Twenty-nine eyes received fewer than 4 injections and in 12 of these, the final was VA < 20 letters, however in the other 17 eyes the median final VA was 76 (55, 80) letters at 12 months. Cataract surgery was performed in 9 ranibizumab-treated eyes and 4 aflibercept eyes with YAG capsulotomy performed in one eye from each group.

4.4.5 Inactivity, Switching and Loss to follow-up

Kaplan-Meier survival analysis was used to compare ranibizumab and aflibercept in terms of time to first grading of inactivity, switching and loss to follow-up (Figure 4.2). Inactivity was recorded at least once in 12 months in 227 eyes (96% of completers), with the first occurrence at a median (Q1, Q3) of 58 (29, 98) days. The Cox-proportional hazards model predicted aflibercept achieved inactivity sooner than ranibizumab ($P = 0.02$).

Thirty-five eyes (12%) switched treatment within 12 months, more commonly from ranibizumab (26 eyes, 21%) than from aflibercept (9 eyes, 5%) ($P < 0.001$) (Table 4.2). The median (Q1, Q3) time to switching for all eyes combined was 155 days (112, 252). Eyes switched from ranibizumab to a dexamethasone implant (6 eyes), to aflibercept (17 eyes) or to bevacizumab (2 eyes) with a median VA of 59 (36, 65) letters at the time of switch. Eyes switched from aflibercept with a lower median VA of 45 (29, 50) letters at the time of switch to a dexamethasone implant (5 eyes) or ranibizumab (4 eyes).

Figure 4.2. Kaplan-Meier curve for first grading of inactivity, time to switching, and dropout by drug.



Sixty eyes (20%) dropped out before 12 months. The non-completion rate was similar in the ranibizumab group (21%) and the aflibercept group (20%). The overall median (Q1, Q3) time

to dropout was 193 days (119, 271). Documented reasons for loss to follow-up included 2 deaths, a medical contraindication in 1 patient, futility of treatment in 3 eyes, 7 patients declined further treatment while 10 patients went to another doctor.

4.4.6 Adverse events

Macular changes affecting vision were newly observed during follow-up in 28 eyes (ERM, macular hole, pigment clumping, atrophy) with a mean (SD) baseline VA of 15 (20) letters and mean 12-month VA of 22 (28) letters. Neovascular complications in either the anterior segment (16 eyes) or posterior segment (17 eyes) led to poor outcomes with a combined mean (SD) VA of 13 (21) letters at 12-months. Eighty-three eyes received pan-retinal photocoagulation with a 12-month mean VA (SD) of 36 (30) letters from a baseline VA of 26 (28.5) letters. Eyes receiving PRP (83 eyes) had fewer injections (SD) with 6.4 (3.4) compared to 7.3 (3) in eyes that did not receive PRP ($P = 0.04$). Vitreous haemorrhage was reported in 13 eyes that received a mean (SD) of 3.8 (2.7) injections. Significantly fewer injections 2.5 (1.6) were given to 16 eyes that developed rubeotic glaucoma compared to the rest of the cohort ($P < 0.001$). Rubeotic glaucoma developed more often in ranibizumab treated eyes (12 eyes vs 4 aflibercept treated eyes; $P = 0.01$) however these eyes received fewer injections 1.8 injections vs. 4.25 injections respectively. Injection numbers overall, irrespective of the agent, were strongly associated with rubeotic glaucoma occurrence ($P < 0.001$) suggesting the injection number rather than the drug was associated with rubeotic glaucoma. There was one retinal detachment with VA at 12 months of light perception but no reported cases of endophthalmitis or traumatic cataract following 1915 injections.

4.5 Discussion

We report significant improvements in VA and reductions in macular thickness in eyes receiving aflibercept or ranibizumab treatment for CRVO in routine clinical practice. Both

groups were well matched for gender, age, visual acuity and CST at baseline. Both groups had similar numbers of visits and injections during the 12-month period. Our comparative analysis found that eyes receiving aflibercept had greater visual gains and reductions in CST.

Significant differences in the molecular structure and mode of action of the drugs we studied may be the reason for the better outcomes we found with aflibercept for CRVO. While ranibizumab is a humanised monoclonal antibody, aflibercept acts as a decoy-receptor for VEGF and may offer superior VEGF suppression due to higher binding affinity against VEGF (Papadopoulos et al., 2012) as well as longer intravitreal half-life (Stewart & Rosenfeld, 2008). This may be particularly important in eyes with CRVO, which have very high vitreous levels of VEGF (Aiello et al., 1994).

While treatment is mandated in RCTs, treatment patterns greatly differ in routine clinical practice due to various factors, including patient compliance, cost, and individual re-treatment preferences. As a consequence, the number of injections is often lower than in RCTs as observed in the current analysis and other database studies (Lotery & Regnier, 2015). Many analyses of outcomes from routine clinical practice have reported 4-5 injections for CRVO in the first year, in contrast to RCTs which gave on average 8.8-9.6 aflibercept injections (Campochiaro et al., 2011) or 8.4 ranibizumab injections (Brown et al., 2013b; Korobelnik et al., 2014b) within the first 12 months. Centres participating in the current analysis gave more injections than have previously been reported from routine clinical practice (a median of 7 for both aflibercept and ranibizumab), which is only slightly fewer than in RCTs.

The combination of stronger and potentially longer VEGF suppression of aflibercept may be one of the main drivers for better clinical outcomes since the more prolonged suppression may compensate for the somewhat lower number of injections. Cystoid macula oedema

secondary to CRVO may be a particularly attractive indication for new longer acting anti-VEGF agents.

Patient population

The patient population in this analysis from routine clinical practice was older (mean 72 years) than patients included in RCTs using aflibercept or ranibizumab (range 61.5 - 69.7 years) (Brown et al., 2013a; Campochiaro et al., 2011; Korobelnik et al., 2014a; Larsen et al., 2018). Patient eyes in the current analysis had worse average baseline VA scores (40.1 letters) than those included in RCTs (range 47.4 – 53 letters), with less thickened mean baseline CST of 615μm (range in RCTs 665 – 693μm) (Brown et al., 2013a; Campochiaro et al., 2011; Korobelnik et al., 2014a; Larsen et al., 2018).

Visual outcomes and macular thickness

Visual outcomes for aflibercept and ranibizumab, both adjusted (16.6 and 9.8) and unadjusted (13.1 and 9.9), from this analysis were slightly inferior to those observed in RCTs (13.9 to 18.9 letters) (Brown et al., 2013b; Campochiaro et al., 2011; Korobelnik et al., 2014b; Scott et al., 2017). Lower gains in vision observed in this study were likely due to differences in baseline characteristics and lack of mandated treatment every 4 weeks in the first 6-months. Also, the time from the occurrence of the CRVO to treatment initiation was not limited as in RCTs. Fundus fluorescein angiography, performed in around 60% of eyes, was evenly distributed between both treatment groups. A total of 7% and 25% of eyes showed signs of macular ischaemia and peripheral ischaemia, respectively. It seems unlikely that eyes with macular ischaemia contributed significantly to the observed reduced VA gains of the total cohort, since previous reports in ranibizumab treated eyes found that macular ischaemia did not influence VA outcomes (Larsen et al., 2016; Tadayoni et al., 2017).

Aflibercept-treated eyes had more significant reductions in CST than ranibizumab-treated eyes. The Cox-proportional hazards model predicted that aflibercept was significantly faster in achieving CMO inactivity than ranibizumab (P = 0.02).

Switching treatments and loss of follow-up

Switching occurred in around 12% of eyes, mainly from ranibizumab (21%) rather than from aflibercept (5%). The reason for switching was not recorded. We hypothesize that it might have included a perceived lack of response by the treating physician. Loss of follow-up was observed in 20% of eyes, which is comparable to other observational studies. Ranibizumab was approved for the treatment of CME secondary to CRVO much earlier than aflibercept. This might have influenced the decision to switch too.

Adverse events

The rate and nature of adverse events, such as macular atrophy, pigment clumping or epiretinal membrane, in our study population was relatively low and about the same as in other diseases treated with intravitreal anti-VEGF such as diabetic retinopathy or age-related macular degeneration.

An important detail is the number of lasers and the fact that, despite anti-VEGF treatment, rubeotic glaucoma developed in 16 eyes – those eyes had significantly fewer injections than the rest of the cohort (mean 2.5 [1.6]). It has now been established that the requirement for panretinal laser photocoagulation in proliferative diabetic retinopathy can be reduced by anti-VEGF therapy (Sivaprasad et al., 2017; Writing Committee for the Diabetic Retinopathy Clinical Research et al., 2015). With the relatively higher VEGF levels in patients with CRVO one might expect a similar benefit from anti-VEGF therapy (Aiello et al., 1994). However, the evidence base is not as clear for the risk of neovascularization in eyes with CRVO receiving anti-VEGF therapy, especially when treatment is stopped. Data from routine clinical practice

may provide useful insights to the development and management of rubeosis in eyes receiving VEGF inhibitors for CRVO.

Strengths and weaknesses

The current analysis has limitations that are inherent to studies using data from routine clinical practice. In contrast to RCTs, treatment decisions are based on the physician's observation in consultation with the patient. The choice of when to treat and to schedule the next appointment also relies on the patient's availability to integrate frequent appointments into a busy work scheduled. Normally, no reading centre recommendations or protocols are followed as is the case in RCTs. There was no randomization to treatment groups, which, while not significant, resulted in some differences in baseline characteristics. We accounted for this partially by adjusting for baseline factors that might impact the outcome, such as age, VA and CST.

The strengths of the current study are the large sample size and an adequate representation of how anti-VEGF drugs are used in routine clinical practice in a number of centres that treat CRVO. The present study, which had fortuitously well-matched baseline characteristics, is unlikely to overestimate either of the drugs' effectiveness (Concato, Shah, & Horwitz, 2000).

Observational studies may suffer from poor data quality. For example, baseline and 12-month visual acuity values could only be identified in around half of the 30,000 otherwise eligible eyes with neovascular age-related macular degeneration in a recent analysis from the IRIS database (Kiss et al., 2020). By contrast, the FRB! database only accepts "finalised" data which is 100% complete and within prespecified ranges, the finalisation rate is consistently above 95%.

Conclusions

This study found that both aflibercept and ranibizumab improved VA and reduced macular thickness over 12 months in eyes with CRVO. Aflibercept led to significantly greater improvements, both in VA and CST. Longer-term observational studies are warranted to verify whether the initial benefit of aflibercept and ranibizumab is maintained.

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CHAPTER 5: TWELVE-MONTH OUTCOMES OF RANIBIZUMAB VERSUS AFLIBERCEPT FOR MACULAR OEDEMA IN BRANCH RETINAL VEIN OCCLUSION: DATA FROM THE FRB! REGISTRY.

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5.1 Abstract

Background/Aims: To compare the efficacy of ranibizumab (0.5mg) to aflibercept (2mg) in the treatment of cystoid macular oedema (CMO) due to branch retinal vein occlusion (BRVO) over 12 months.

Methods: A multicentre, international, database observational study recruited 322 eyes initiating therapy in real-world practice over 5 years. The main outcome measure was mean change in EDTRS letter scores of visual acuity (VA). Secondary outcomes included anatomic outcomes, percentage of eyes with VA > 6/12 (70 letters), number of injections and visits, time to first inactivity, switching or non-completion.

Results: Generalised mixed effect models demonstrated that mean (95% CI) adjusted 12-month VA changes for ranibizumab and aflibercept were similar (+10.8 [8.2, 13.4] versus +10.9 [8.3, 13.5] letters respectively, P = 0.59). The mean adjusted change in central subfield thickness (CST) was greater for aflibercept than ranibizumab (-170 [-153, -187] µm versus -147 [-130, -164] µm respectively, P = 0.001). The overall median (Q1, Q3) of 7 (4, 8) injections and 9 (7, 11) visits was similar between treatment groups. First grading of inactivity occurred sooner with aflibercept (P = 0.01). Switching was more common from ranibizumab (37 eyes, 23%) than from aflibercept (17 eyes, 11%; P = 0.002).

Conclusion: Visual outcomes at 12 months in this direct comparison of ranibizumab and aflibercept for BRVO in real world practice were generally good and similar for the 2 drugs, despite a greater effect of aflibercept on CST and time to first grading of inactivity.

Introduction

Randomised controlled trials (RCTs) have provided the safety and efficacy data for ranibizumab and aflibercept to become first-line treatments recommended in international guidelines for cystoid macular oedema (CMO) secondary to branch retinal vein occlusion (BRVO) (Brown et al., 2011; Campochiaro et al., 2015; Campochiaro et al., 2010; Clark et al., 2016; Flaxel et al., 2020; Schmidt-Erfurth et al., 2019; Shalchi, Mahroo, Bunce, & Mitry, 2020). Less is known about the outcomes in real-world clinical practice. Evidence from routine care can complement RCTs since they have higher levels of external validity that is more generalisable to the broader population (Booth & Tannock, 2014).

Current evidence derived from routine care regarding vascular endothelial growth factor (VEGF) inhibitors for BRVO includes a heterogeneous series of retrospective reviews, mainly in single centres, studying various treatment regimens, often in combination with, or compared to, laser or steroids. Most studies concern ranibizumab and bevacizumab (Brynskov, Kemp, & Sørensen, 2014; Buyru Özkurt, Akkaya, Aksoy, & Şimşek, 2018; Chatziralli et al., 2018; Hasegawa, Takahashi, Maruko, Kogure, & Iida, 2019; Khan et al., 2017; Lalinská, Krásný, Studený, & Veith, 2018; Miwa et al., 2017; Osaka et al., 2018; Ozkaya, Tarakcioglu, & Tanir, 2018; Shiono et al., 2018; Son, Kwak, Kim, & Yu, 2017; Wang et al., 2016; Winterhalter et al., 2018). A systematic review of real world BRVO studies concluded that the visual and anatomic improvements were less impressive than in RCTs, with fewer injections in the real-world studies (Ang et al., 2020).

The UK EMR Users Group recently reported outcomes of treatment with either anti-VEGF, steroids or laser in 5661 patients with BRVO, with 80% loss to follow-up at 12 months (Gale et al., 2020). The LUMINOUS study enrolled 326 eyes with treatment naive BRVO receiving ranibizumab with 54% loss to follow up at 12 months (Pearce et al., 2020).

The Fight Retinal Blindness outcomes registry has provided data on real-world outcomes for neovascular age-related macular degeneration (Bhandari, Nguyen, Arnold, et al., 2020; Gillies et al., 2019; Gillies et al., 2016), and for diabetic macular oedema treated with VEGF inhibitors (Bhandari, Nguyen, Fraser-Bell, et al., 2020). The aims of this study were to report real world outcomes and comparative analysis of ranibizumab and aflibercept, in treatment-naïve eyes with CMO due to BRVO using observational data tracked in a large international patient registry.

5.2 Materials And Methods

5.2.1 Design and setting.

This was an international, multicentre, retrospective study using data from the Retinal Vein Occlusion module of the web-based Fight Retinal Blindness! Registry (Gillies et al., 2014). The study adhered to the tenets of the Declaration of Helsinki and followed the STROBE checklists for reporting observational studies (von Elm et al., 2008). Local ethics and data protection approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists and the University of Sydney Human Research Ethics Committees (HREC#16.09), the Caldicott Guardian (Dr Kilian Hynes) of the Royal Free London NHS Foundation Trust, Institutional Review Boards of the Mater Private Hospital (IRB, 1/378/2130) in Dublin, Ireland; the Hospital Clinic of Barcelona, Spain (2015/57-OFT-HUSC) and the Société Française d'Ophtalmologie (2017_CLER-IRB_II-05) in Paris, France. All patients gave their informed consent. This consisted of opt-in consent from patients in France, Ireland, Spain and UK; while the ethics committee in Australia approved the use of opt-out patient consent.

5.2.2 Data Sources and Measurements

Treatment decisions and timing were at the discretion of the physician and patient, reflecting routine clinical practice. Mandatory data points were populated at each clinical visit via a web-based interface. Variables were either numeric, mutually exclusive or a selection from a drop-down menu. Logarithm of the minimum angle of resolution (log MAR) visual acuity (best of uncorrected, corrected or pinhole) was expressed in letters read on an EDTRS chart. Macular oedema, including central subfield thickness (CST in μm), was assessed with optical coherence tomography using the same machine for the same patient throughout. The presence of CMO (active or inactive) was judged by the practitioner. Other observations recorded at each visit included any treatments given, other procedures performed and adverse events. Enrolment in the audit required a baseline visit when the first injection was administered that had extra data points regarding demographics, the type of RVO, presence or absence of key risk factors and ischaemia if fluorescein angiography was performed.

5.2.3 Patient selection

We studied treatment-naïve patients with CMO due to BRVO that commenced treatment with either aflibercept (2mg Eylea, Bayer) or ranibizumab (0.5mg Lucentis, Genentech Inc/Novartis) between 1st June 2014 and 1st June 2019. Central and Hemi-retinal vein occlusions were excluded. Eligible patients must have had at least three visits to establish sufficient ongoing follow-up. "Completers" were defined as having ≥ 12 months of follow-up. We defined “switchers” as eyes that received at least 2 injections of an alternative agent.

5.2.4 Outcomes

The primary outcome measure was mean change from baseline VA at 12 months. Secondary outcomes included mean change in CST, visits, injections and the proportion of eyes with VA > 6/12 (70 letters). Event based outcomes included time to first grading of

inactivity, switching drugs and non-completion over 12 months. Outcomes were studied overall and comparatively between ranibizumab and aflibercept.

5.2.5 Statistical analysis

Baseline and demographic characteristics were summarised with descriptive statistics, including counts and percentages for categorical variables; and mean, standard deviation (SD), median, first and third quartiles (Q1, Q3) for continuous variables. Observations began at the first treatment visit and continued until the 12-month visit (365 +/- 30 days). We compared baseline characteristics of the ranibizumab and aflibercept groups with t-tests, Wilcoxon signed-rank tests, Chi-square tests and Fisher's exact tests where appropriate. Crude visual and anatomic outcomes used the last observation carried forward (LOCF) for non-completers and switchers. The last observation in switchers was when the first treatment with the alternative agent was delivered.

Generalised additive mixed effects models were used to compare longitudinal changes in VA and CST with the interaction between treatment and time as the main predictor. We included adjustments for age and baseline VA or CST as fixed effects, while nesting of outcomes within doctor and patient (bilateral cases) were included as random effects. The longitudinal models included all eyes but did not include visits after the first alternative agent was delivered in switchers. The longitudinal models were plotted and analysed to compare adjusted VA and CST outcomes for each drug.

Number of injections and visits were calculated for completers but also compared by group in all eyes up to completion, non-completion or switching with generalised Poisson mixed models with an offset for log days of follow-up. Kaplan-Meier survival curves were generated for time to switching, non-completion and first physician grading of CMO inactivity. The time to inactivity for each agent was compared with a Cox-proportional hazards model. Age,

baseline VA and baseline CST were considered fixed effects, while random effects addressed nesting under each physician's care or within a single patient (bilateral cases).

Analysis was performed in R version 4.0.0 (cran.r-project.org) utilising the *glmmTMB* (1.0.1) and *mgcv* (V1.8-31) packages for generalised linear and generalised additive mixed models respectively (R Core Team, 2020). The *survival* (3.1-12) package was used to generate the Kaplan Meier estimates, and *coxme* (2.2-16) for Cox mixed effects models (R Core Team, 2020).

5.3 Results

5.3.1 Study participants

We identified 322 treatment naïve eyes with CMO due to BRVO that started treatment with ranibizumab (162 eyes) or aflibercept (160 eyes) between June 1, 2014, and June 1, 2019 (Table 5.1).

Baseline demographic characteristics were broadly similar between the 2 treatment groups. The mean baseline visual acuity (SD) was around 6/24 and was slightly higher in the aflibercept group, but this was not significant (ranibizumab 54.3 [19.4] letters vs. aflibercept 56.9 [18.7]; P = 0.21). The mean baseline CSTs (SD) were also similar (ranibizumab 475µm [164] vs. aflibercept 456µm [148]; P = 0.30).

Table 5.1. Baseline characteristics of all treatment naïve BRVO eyes commencing treatment with ranibizumab or aflibercept.

	Overall	Ranibizumab	Aflibercept	P-value
Eyes, n	322	162	160	
Patients, n	319	162	157	
Female, % patients	54%	50%	57%	0.22
Age, mean (SD)	70 (12)	70 (13)	71 (11)	0.44
VA, mean (SD)	55.6 (19.1)	54.3 (19.4)	56.9 (18.7)	0.21
≥ 70 letters (6/12), %	30%	28%	32%	0.58
≤ 35 letters (6/60), %	16%	17%	14%	0.68
FFA Performed, n (%) *	151 (47%)	84 (52%)	67 (42%)	0.09
Macular Ischaemia, n (%)	16 (5%)	10 (6%)	6 (4%)	0.75
Peripheral Ischaemia, n (%)	49 (15%)	30 (19%)	19 (12%)	0.43
CST, mean (SD)	466 (156)	475 (164)	456 (148)	0.30
Hypertension, %	68%	70%	66%	0.35
Glaucoma, %	8%	7%	8%	0.97
Country, %				
Australia	36%	33%	39%	
France	13%	15%	11%	
Ireland	9%	9%	9%	
United Kingdom	20%	18%	22%	
Spain	21%	25%	18%	

n = Number, SD = Standard Deviation, VA = Visual Acuity (log MAR letters), FFA = Fundus Fluorescein Angiography, CST = Central Subfield Thickness (in microns). *Not mandatorily performed or documented.

5.3.2 Visual outcomes

The crude, unadjusted mean 12-month VA change (95% CI) was +13.0 (10.1, 15.9) letters for ranibizumab vs. +10.9 (8.4, 13.4) for aflibercept (P = 0.80) (Table 5.2).

Around 40% of eyes gained ≥ 15 letters (ranibizumab 41% vs. aflibercept 40% [P = 0.98]) and 60% of eyes had 12-month VA > 6/12 (ranibizumab 59% vs. aflibercept 61% [P = 0.80]) compared with 30% at baseline (ranibizumab 28% vs. aflibercept 32% [P = 0.58]). Fourteen eyes (4%, 7 eyes from each group) lost ≥ 15 letters with mean VA decreasing from 58 letters at baseline to 35 letters (6/60) at 12 months. Eighteen eyes had a final VA ≤ 6/60 after 12 months (ranibizumab 8 [6%] vs. aflibercept 10 eyes [7%]; P = 0.80), but these eyes started

with a mean baseline VA of 6/60. Individual eyes that had poor outcomes are discussed below in *Adverse events*.

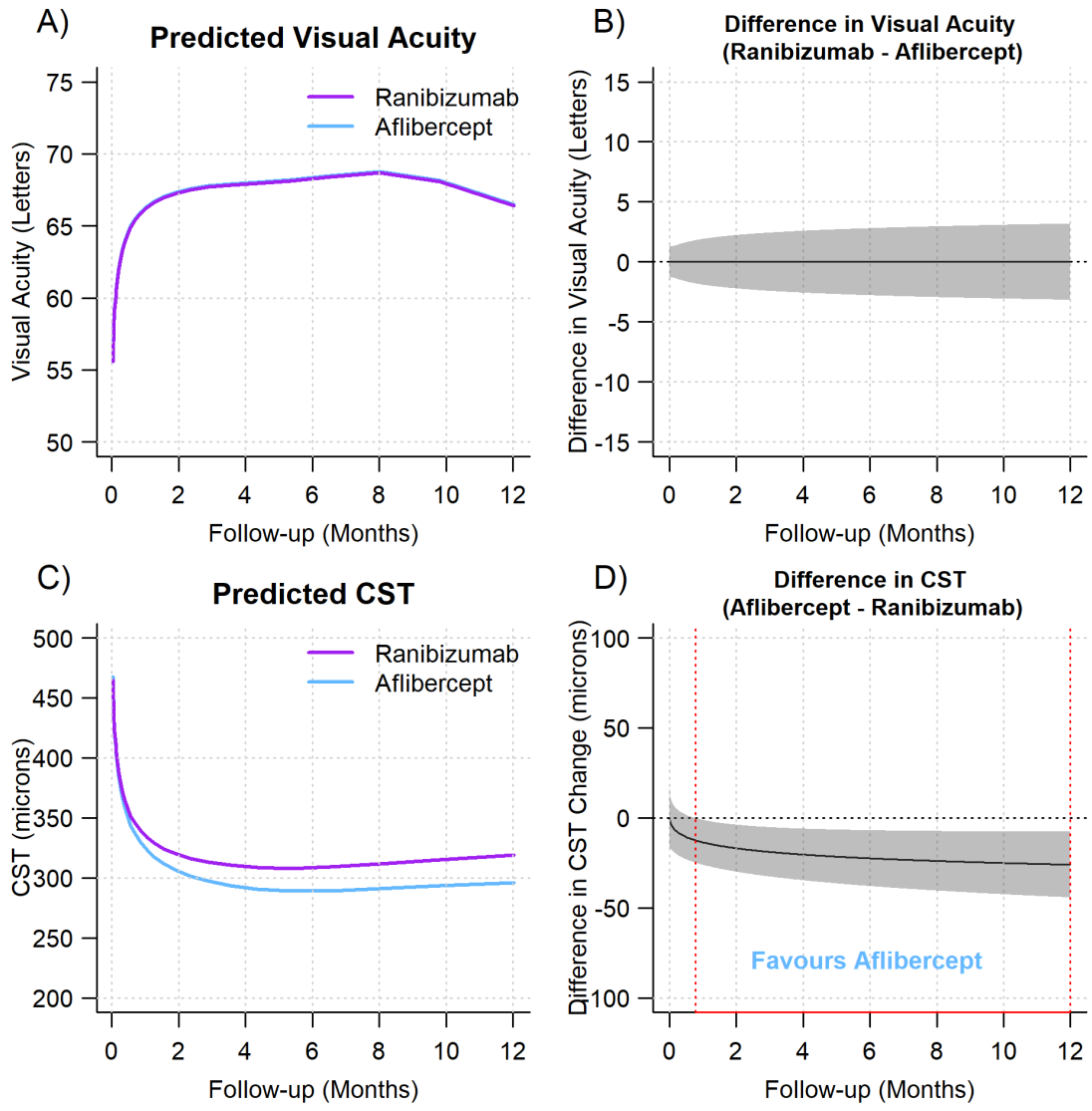
The mean VA change (95% CI) adjusted using the generalised additive mixed model described in *Methods* was +10.8 (8.2, 13.4) letters in the ranibizumab group vs. +10.9 (8.3, 13.5) for aflibercept [P = 0.59]. The mean adjusted VA over 12 months for each group is shown in Figure 5.1A. Adjusted mean VA change peaked at around 8 months (+13.1 (10.9, 15.3) letters for ranibizumab, +13.2 (10.9, 15.4) for aflibercept) with some erosion of those gains out to 12 months. Subtracting the ranibizumab model from the aflibercept model, Figure 5.1B shows similar predicted mean VA changes between the 2 treatment groups over 12-months.

Table 5.2. 12-Month outcomes in BRVO eyes - Overall and stratified by anti-VEGF agent received. Significant P-values comparing ranibizumab and aflibercept are highlighted in bold.

	Overall	Ranibizumab	Aflibercept	P-value
Eyes, n	322	162	160	
Baseline VA, mean (SD)	55.6 (19.1)	54.3 (19.4)	56.9 (18.7)	0.21
Final VA, mean (SD)	67.6 (17.9)	67.3 (18)	67.8 (17.8)	0.80
Crude VA change, mean (95% CI)	12.0 (10, 13.9)	13.0 (10.1, 15.9)	10.9 (8.4, 13.4)	0.28
Adjusted VA change, mean (95% CI) [α]		10.8 (8.2, 13.4)	10.9 (8.3, 13.5)	0.59
Gained ≥ 15 letters (%)	40%	41%	40%	0.98
Lost ≥ 15 letters (%)	4%	4%	4%	1.00
VA ≥ 70 %Baseline / %Final	30 / 60	28 / 59	32 / 61	0.58/0.80
VA ≤ 35 %Baseline / %Final	16 / 6	17 / 6	14 / 7	0.68/0.80
CST Baseline, mean (SD)	466 (156)	475 (164)	456 (148)	0.30
CST Final, mean (SD)	310 (104)	317 (109)	303 (98)	0.23
CST Change, mean (95% CI)	-155 (-173, -137)	-158 (-182, -133)	-153 (-180, -127)	0.81
Adjusted CST Change, mean (95% CI)		-147 (-130, -164)	-170 (-153, -187)	0.001
Completers, n (%)	259 (80)	130 (80)	129 (81)	0.93
Switchers, n (%)	54 (17)	37 (23)	17 (11)	0.002
Lost to follow up, n (%)	63 (20)	32 (20)	31 (19)	
Injections, median (Q1, Q3) *	7 (4, 8)	6 (4, 9)	7 (4, 8)	0.75
Visits, median (Q1, Q3) *	9 (7, 11)	9 (7, 11)	9 (8, 12)	0.80

n – Number, VA – Visual Acuity, SD – Standard Deviation, CI – Confidence Interval, CST – Central Subfield Thickness, Q1 – First Quartile, Q3 – Third Quartile. All Eyes – Includes completers, switchers and Non-completers. "Completers" – Eyes with 12 months of observation from the start of treatment, "Switchers" – Eyes receiving ≥2 injections of the other treatment drug prior to completion of 12 months from the start of treatment. Observations were included in the analysis only up to the first occurrence of switching agents. "Non-Completers" – Eyes not completing 12 months of observations from the start of treatment. * Last observation carried forward for switchers and non-completers. [α] Calculated from longitudinal models adjusting for age and baseline VA (fixed effects), and practice and intra-patient correlation for bilateral cases (random effects).

Figure 5.1. Predictions from longitudinal generalised additive models of adjusted visual acuity (A and B) and central subfield thickness (CST) (C and D) by drug. Red dotted lines in (D) indicate periods in which the CI of the difference between drugs no longer crosses zero



5.3.3 Macular thickness

Both drugs were effective in reducing macular thickness (Table 5.2). Mean unadjusted final CST (SD) was slightly lower in the aflibercept group at 303 (98) µm *vs.* 317 (109) µm in the ranibizumab group [P = 0.23]. The unadjusted change in CST was similar between drugs but after adjusting for baseline CST and age, the mean adjusted CST change (95% CI) was significantly greater for eyes in the aflibercept group at -170 (-153, -187) µm *vs.* -147 (-130, -164) µm in the ranibizumab group [P = 0.001]. The statistically significant longitudinal trend favouring aflibercept is shown in Figure 5.1C-1D.

5.3.4 Treatments and visits

Completers (80%) had a median (Q1, Q3) of 7 (4, 9) injections over a median (Q1, Q3) of 9 (7, 11) visits without any significant difference between agents (P = 0.75 and P = 0.80, respectively) (Table 5.2). The median intervals between the 1st to 5th injections were 28, 28, 42 and 42 days in both groups. The mean number of injections given between 6 and 12 months was 1.9 (2.0 on aflibercept, 1.9 on ranibizumab). Sixty-nine eyes with complete follow-up (27%) had a median final VA of 6/9.5 after receiving ≤ 3 injections over 12 months, as did 78 eyes (31% of completers) that had no injections in the final 6 months. Macular laser was applied to 7 eyes (2%) during the 12 months at a median of 105 days; to 4 eyes in the ranibizumab group, and 3 eyes in the aflibercept group.

5.3.5 Inactivity, Switching and Loss to follow-up

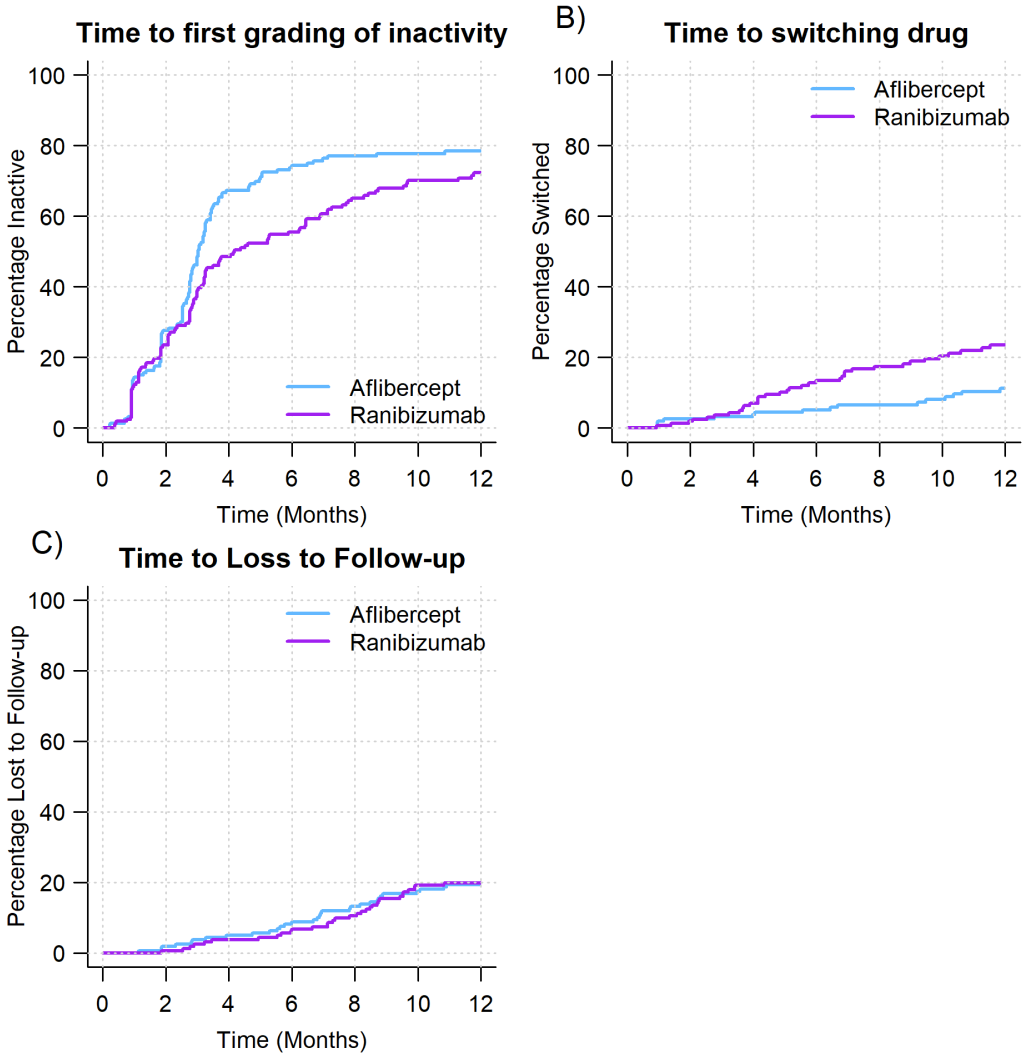
Time to first grading of inactivity, switching and loss to follow-up were analysed with Kaplan-Meier estimates to compare agents (Figure 5.2). A first grading of inactivity with aflibercept was more likely to occur over time than with ranibizumab after adjustment with the Cox-proportional hazards model (P = 0.01). The median (Q1,Q3) time to inactivity for eyes receiving aflibercept was 84 (56, 100) days *vs.* 88 (41, 159) days for ranibizumab.

Fifty-four eyes (17%) switched treatment within 12 months (Table 5.2). Switching was more common in the ranibizumab group (37 eyes, 23%) than in the aflibercept group (17 eyes, 11%; P = 0.002). Thirty-two eyes from the ranibizumab group eyes switched to aflibercept and 5 switched to a dexamethasone implant. Seven aflibercept eyes switched to ranibizumab, 2 to bevacizumab and 6 to a dexamethasone implant. Overall switching within the first 12 months occurred after a median (Q1, Q3) of 172 (111, 285) days. The median (Q1, Q3) VA at the time of switching was around 6/15, with 65 (50, 70) letters in the

ranibizumab group and 68 (58, 75) letters in the aflibercept group. The 11 eyes overall that switched to dexamethasone also had VA around 6/15 or 65 (55, 73) letters when they switched at a median of 280 (151, 332) days.

Sixty-three eyes (20%) did not complete 12 months of follow-up, with similar rates in the ranibizumab (20%) and aflibercept group (19%). The overall median (Q1, Q3) time to dropout was 217 days (156, 266) with a median VA (Q1, Q3) before dropout of 72 (58, 81) letters (approx. 6/12 [6/19, 6/7.5]). Documented reasons for loss to follow-up included 3 deaths, 6 patients declined further treatment, further treatment was considered futile in 1 eye, while 7 patients went to another doctor.

Figure 5.2. Kaplan-Meier curve for (A) first grading of inactivity, (B) time to switching and (C) dropout by initial injection.



5.3.6 Adverse events

Macular changes affecting vision occurred during the study in 24 eyes (epiretinal membrane, macular hole, pigment clumping, atrophy). The median VA (Q1, Q3) at 12 months in this group was around 6/19 or 60 (44, 69) letters but did include three of the eyes that lost ≥ 15 letters and 4 eyes that had a final VA of ≤ 6/60. Posterior segment neovascularisation was reported in 1 eye, but 35 eyes (21 ranibizumab, 14 aflibercept; P = 0.3) received sector photocoagulation at a median (Q1, Q3) of 106 (49,225) days. These eyes still received a median of 8 (5, 9) injections over 12 months and were confined to five centres (18%). Vitreous haemorrhage occurred in 2 eyes. There was 1 reported case of infectious endophthalmitis with a final VA of count fingers, but no traumatic cataract or retinal detachment with a total of 1979 injections.

5.4 Discussion

This analysis of treatment outcomes using data from an observational database found that aflibercept and ranibizumab were both effective at improving visual acuity and reducing macular thickness in patients with BRVO 12 months after initiation of treatment. The mean unadjusted and adjusted VA changes were +13.0 and +10.8 letters respectively for ranibizumab and were both +10.9 letters for aflibercept (P = 0.17, 0.86). Aflibercept was significantly more effective at reducing macular thickness than ranibizumab. The mean final CSTs for aflibercept and ranibizumab were 303µm vs. 317µm and the adjusted CST changes were -170µm vs. -147µm respectively (P = 0.23, 0.001). Both groups had a median of 7 injections over a similar number of visits. Extension of the interval to 6 weeks after three monthly injections was apparent. On average only 2 injections were given per eye in the final 6 months. Posterior segment neovascularisation may have been underreported (one eye). Laser was possibly used to treat retinal ischaemia without neovascularisation in 35 eyes confined to a few centres but without a reduced number of injections.

Ranibizumab (0.5mg) given monthly in the first 6 months in the BRAVO study led to a mean improvement in visual acuity of +18.3 letters and a reduction of CST of -345 µm (Campochiaro et al., 2010). Similar changes were reported for monthly aflibercept in the VIBRANT study (+17 letters and -280 µm) (Campochiaro et al., 2015). Vision gains were maintained at 12 months with flexible or bimonthly treatment, essentially totalling 8.8 and 9.0 injections in the first year of treatment (Brown et al., 2011; Clark et al., 2016). The 2-year BRIGHTER study reported 16 letter gains in VA with a flexible ranibizumab regime after 3 dose loading (Tadayoni et al., 2017). An ongoing need for VEGF suppression in many eyes with BRVO beyond 6 months was demonstrated in BRAVO, VIBRANT. In the present study, a mean of 1.9 injections given in the second 6 months may account for the erosion of the peak visual gains seen at 8 months.

The mean baseline CST was low in our study (465 µm) compared to BRAVO (551 µm), BRIGHTER (530-550 µm) and VIBRANT (559 µm) possibly leaving less room for improvement. The baseline vision in our cohort (56 letters), was better than BRAVO (53 letters) but worse than in VIBRANT (58 letters) and BRIGHTER (60 letters). The proportion of eyes achieving 12-month VA > 6/12 (70 letters) in the present study was 60% compared to 65% in BRAVO and 85% in VIBRANT.

Under-treatment is typically blamed for less impressive outcomes in the real-world setting (Kiss et al., 2014). A systematic review of real-world BRVO outcomes analysed 13 ranibizumab treatment arms in various case series and comparative studies involving anti-VEGF, laser or steroids (Ang et al., 2020; Brynskov et al., 2014; Buyru Özkurt et al., 2018; Chatziralli et al., 2018; Hasegawa et al., 2019; Khan et al., 2017; Lalinská et al., 2018; Miwa et al., 2017; Osaka et al., 2018; Ozkaya et al., 2018; Shiono et al., 2018; Son et al., 2017; Wang et al., 2016; Winterhalter et al., 2018). From a baseline of 54 letters and CST of 501 µm, the authors estimated a weighted mean VA change of +15.9 letters, mean CST change of -189.8 µm, and a mean of 4.9 ranibizumab injections at 12 months. The studies selected

for the meta-analysis still had some artifice placing them somewhere between the real-world and RCTs, for example, many excluded patients with common co-existent retinal pathology (Brynskov et al., 2014; Buyru Özkurt et al., 2018; Hasegawa et al., 2019; Miwa et al., 2017; Osaka et al., 2018; Ozkaya et al., 2018; Shiono et al., 2018; Son et al., 2017; Wang et al., 2016), a media opacity or a history of intraocular surgery (Buyru Özkurt et al., 2018; Chatziralli et al., 2018; Hasegawa et al., 2019; Miwa et al., 2017; Osaka et al., 2018; Son et al., 2017), limits were placed on duration of disease (Brynskov et al., 2014; Buyru Özkurt et al., 2018; Miwa et al., 2017; Osaka et al., 2018; Ozkaya et al., 2018; Shiono et al., 2018; Son et al., 2017; Wang et al., 2016; Winterhalter et al., 2018), and they typically followed a protocol which demanded comprehensive investigations at specific time points (Buyru Özkurt et al., 2018; Hasegawa et al., 2019; Miwa et al., 2017; Osaka et al., 2018; Ozkaya et al., 2018; Shiono et al., 2018; Son et al., 2017; Wang et al., 2016).

Real-world evidence in its purest form should be derived in a setting indistinguishable from normal practice. Previous studies using extracted data from medical records or from a registry have suffered from poor follow-up. The UK EMR Users Group reported vision gains of +9.6 letters with 5.1 injections in the 26% of 3939 eyes with follow-up at 12 months (Gale et al., 2020). The Luminous BRVO study reported +11.9 letter gains with 5.0 injections but also suffered from relatively high loss to follow-up (> 50%) (Pearce et al., 2020). In our study the relatively good visual acuity, at last observation in eyes (20%) that did drop out, of 72 (58, 81) letters suggests that some may have been successfully treated.

There are some limitations in this study in keeping with its observational design. We did not track time from first symptoms, however the mean visual acuity at the time of the first injection was similar to BRAVO and VIBRANT, suggesting there were no untoward delays in starting treatment. The reason for the choice of one drug over the other is not known in each case although the drug groups had similar baseline characteristics despite lack of randomisation. Regardless, we adjusted for baseline VA, age, CST and nesting within

practices in our statistical models. Censoring observations after switching may selectively bias results by removing eyes doing poorly, however, the median VA of the eyes that switched at 65 letters (6/15) was not consistent with this. Eyes that switched to a steroid may have done so for the extended duration rather than a poor visual outcome.

Treatment-naïve BRVO eyes receiving VEGF inhibitors in the routine clinical practice have good outcomes – but still lag behind those of the RCTs. Ranibizumab and aflibercept produced equivalent improvements in visual acuity, despite a greater effect on macular thickness and lesser time to first grading of inactivity afforded by aflibercept. The findings are in keeping with similar observational studies that have demonstrated equivalent efficacy of aflibercept and ranibizumab for neovascular age-related macular degeneration (Bhandari, Nguyen, Arnold, et al., 2020; Gillies et al., 2019; Gillies et al., 2016), and also concur with the greater reductions in CST from aflibercept over ranibizumab in diabetic macular oedema (Bhandari, Nguyen, Fraser-Bell, et al., 2020). An ongoing need for VEGF suppression from 6 to 12 months was evident. Visual acuity gains eroded in the last 6 months when only 1.9 injections were given. Further studies are required to investigate the long-term outcomes of BRVO treatment in routine clinical practice beyond 12-months.

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CHAPTER 6: ONE-YEAR REAL-WORLD OUTCOMES OF BEVACIZUMAB FOR THE TREATMENT OF MACULAR OEDEMA SECONDARY TO RETINAL VEIN OCCLUSION.

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6.1 Abstract

Background: Bevacizumab is the only agent that many people can afford, yet there are only limited data on whether it improves macular oedema (MO) secondary to retinal vein occlusion (RVO) in real-world clinical practice. Here we studied 12-month real-world treatment outcomes of bevacizumab for RVO-related MO.

Methods: This was a multicentre, observational study analysing 12-month data from the Fight Retinal Blindness! (FRB) database. We studied treatment-naïve eyes with MO secondary to RVO commencing bevacizumab therapy between June 2009 and June 2019. Visual acuity (VA) and central subfield thickness (CST) were measured at baseline, 6 and 12 months. The primary outcome was a change in VA from baseline to 12 months.

Results: Two hundred and twenty treatment naive eyes were analysed. The baseline VA for BRVO was better than CRVO (55.8 vs. 42.6 LogMAR letters) and this gap widened over the 12-month period, with a 12-month VA change of +14.0 (95% CI 11.1, 16.8) letters for BRVO and + 11.9 (95% CI 6.4, 17.4) for CRVO. The mean CST at baseline was 511 µm for BRVO and 627 µm for CRVO, falling at 12 months by -155 µm (-190, -121) in BRVO and -198 µm (-252, -145) in CRVO. The median number of injections for BRVO and CRVO completers was 7 (5, 9).

Conclusions: Bevacizumab can be an effective treatment of RVO-MO in a real-world setting with outcomes approaching those reported by the seminal clinical trials. The functional and anatomical outcomes of intravitreal therapy were better for BRVO than CRVO.

6.2 Introduction

Bevacizumab is the only anti-VEGF agent that is on the WHO's list of essential medicines (WHO, 2019), and whilst there is a growing body of real-world evidence supporting its use in neovascular macular degeneration and diabetic maculopathy (Gillies et al., 2014; Hunt et al., 2021), there is a paucity of data on its effectiveness in retinal vein occlusion (RVO).

Randomised controlled trials (RCTs) have established VEGF inhibitors as first-line treatment of macular oedema (MO) associated with branch and central RVO, improving and maintaining visual acuity (VA), whilst reducing central subfield thickness (CST) (Brown et al., 2010; Campochiaro et al., 2010). Whilst limited clinical studies suggest that bevacizumab may be as efficacious as ranibizumab and aflibercept (Hykin et al., 2019; Kornhauser et al., 2016), there remains a pressing need to evaluate the effectiveness of bevacizumab at treating MO associated with RVO in real- world practice.

The Fight Retinal Blindness! (FRB!) Registry is an international collaboration collecting real-world data on patients with a range of retinal diseases and it has been used by clinicians in both Australia and New Zealand for the past decade. Bevacizumab remains the first-line treatment for RVO-associated MO in New Zealand and was first-line in Australia until late 2016 (Health) and thus data from Australasia providers using FRB! provide a unique opportunity to evaluate the effectiveness of bevacizumab in the management of RVO. In this study data from FRB! were analysed with the aim of reporting the VA and anatomic outcomes and the frequency of bevacizumab injections over the first year of treatment in eyes with RVO in a real-world setting.

6.3 Methods

6.3.1 Design and setting

Multicentre, observational cohort study examining 12-month routine clinical outcomes in treatment naïve patients with RVO receiving bevacizumab within Australia and New Zealand using data from the FRB! Registry. Treatment decisions were the responsibility of the physician reflecting routine clinical care. FRB! registry has a baseline enrolment visit which establishes the type of RVO (Branch, Hemi or Central RVO) and records data from each clinical visit, including the logarithm of the minimum angle of resolution (LogMAR) VA in letters (best of uncorrected, corrected and pinhole), the presence of MO, CST (µm), treatments given, procedures per- formed, and adverse events. The Royal Australian and New Zealand College of Ophthalmologists and the University of Sydney Human Research Ethics Committees granted ethics approval including the use of opt-out patient consent. The research followed the STROBE guidelines for the reporting of observational studies and adhered to the tenets of the Declaration of Helsinki (von Elm et al., 2008).

6.3.2 Patient selection

The analysis was limited to treatment-naïve patients with RVO that commenced treatment for MO with intravitreal bevacizumab of 1.25 mg (0.05 ml) between 1 June 2009 and 1 June 2019. Patients must have had three or more visits and at least two injections to be included. Eyes with ≥ 12 months of follow-up were defined as ‘Completers’. ‘Switchers’ were defined as eyes receiving at least two injections of an alternative agent within 12-months. Eyes with CRVO or BRVO were included in this analysis. Eyes with Hemi-RVO were excluded. Exclusion criteria include prior vitrectomy, prior laser treatment, prior anti-VEGF or intravitreal steroid treatment.

6.3.3 Outcomes

The primary outcome was mean change in VA from baseline to 12-months. Secondary outcomes included mean change in CST, number of visits and injections, the proportion of eyes with VA > 70 letters. CRVO patients were subdivided by baseline VA, which was used as surrogate marker for ischaemic versus non-ischaemic CRVO as angiographic data were not available for most patients. Time to event analysis over 12 months included first grading of inactivity, switching and non-completion. The grading of lesion activity was performed at all full assessment visits by the attending Clinician. 'Inactivity' was defined by the absence of subretinal and intraretinal fluid. Outcomes were studied for BRVO and CRVO and included sub-groups with baseline VA ≤20 letters and VA > 20 letters with CRVO.

6.3.4 Statistical analysis

Descriptive statistics included the mean, standard deviation (SD), median, and first and third quartiles (Q1, Q3) for continuous variables and counts and percentages for categorical variables. The baseline visit was defined by the receipt of the first treatment. Observations continued until the final visit closest to 12-months (365 ± 30 days). Last observation carried forward (LOCF) was used for non-completers and switchers to calculate crude visual and anatomic outcomes. In switchers, this was the visit at which the alternative agent was first administered.

Longitudinal changes in VA and CST were visualised using generalised additive mixed effect models and included all visits up until either completion, non- completion or the first occurrence of alternative intravitreal agent administered in switchers without imputation of missing data. Analysis was performed in R version 4.0.0 and RStudio version 1.2.5042 utilising the glmmTMB (1.0.2.1) and mgcv (V1.8–33) packages for generalised linear and generalised additive mixed models, respectively. The survival (3.2–7) package was used to generate the Kaplan Meier estimates (R Core Team, 2020).

6.4 Results

6.4.1 Study participants

Table 6.1. Demographic characteristics of all eyes, BRVO, CRVO including CRVO split into subgroups with baseline VA ≤ 20 and VA > 20 letters.

	All eyes	BRVO	CRVO	CRVO ≤ 20 letters	CRVO > 20 letters
Eyes, n	220	135	85	22	63
Patients, n	218	133	85	22	63
Female, %	44%	51%	33%	41%	30%
Age, mean y (SD)	71 (11.7)	72 (11.1)	70 (12.5)	72 (15.1)	69 (11.5)
VA, mean (SD)	50.7 (22.8)	55.8 (18.6)	42.6 (26.4)	4 (3.9)	56 (14.9)
VA > 70 letters, %	21%	22%	20%	0%	27%
VA ≤ 35 letters, %	23%	14%	37%	100%	14%
FFA performed n (%) *	57 (26%)	37 (27%)	20 (24%)	3 (14%)	17 (27%)
Macular ischaemia, n (%)	12 (6%)	10 (7%)	2 (2%)	1 (5%)	1 (2%)
Peripheral ischaemia, n (%)	17 (8%)	13 (10%)	4 (5%)	2 (9%)	2 (3%)
CST, mean (SD)	556 (211)	511 (187)	627 (227)	722 (311)	595 (183)
Hypertension, %	69%	74%	60%	55%	62%
Glaucoma, %	8%	7%	9%	9%	10%
Country, %					
New Zealand	53%	53%	53%	50%	54%
Australia	47%	47%	47%	50%	46%

n – Number, y – years, SD – Standard Deviation, VA – Visual Acuity in log MAR letters, FFA – Fundus Fluorescein Angiography, CST – Central Subfield Thickness (in microns). *Not mandatorily performed or documented.

There were 220 treatment naïve eyes that started treatment with bevacizumab for MO due to BRVO (135 eyes) or CRVO (85 eyes, 22 with VA ≤20 letters and 63 eyes with VA > 20 letters) between June 2009 and June 2019 (Table 6.1). Patients with HRVO, n = 17, were excluded from the analysis subset due to growing evidence that they behave differently from both CRVOs and BRVOs.14 The median/mean baseline VA (SD) were 60/55.8 (18.6) letters in BRVO and 49/42.6 (26.4) letters in CRVO. The means (SD) of baseline CST (SD) were 511 (187) µm for BRVO and 627 (227) µm for CRVO. A higher mean CST of 722 (313) µm

was found in the subgroup of 22 CRVO eyes presenting with VA ≤20 letters. Mean (SD) age at presentation was 7211 years of age in BRVO and 7013 years in CRVO. There were more males only in the CRVO cohort (67% male). Fundus fluorescein angiography was performed in 37 (27%) BRVO eyes and 20 (24%) CRVO eyes. Systemic hypertension and glaucoma were present in 74% and 7% of BRVO eyes, respectively, and 60% and 9% of CRVO eyes.

6.4.2 Outcomes

The crude mean 12-month VA change (95% CI) was +14 (11.1, 16.8) letters in eyes with BRVO and + 11.9 (6.4, 17.4) letters for CRVO eyes (Table 6.2). Most VA improvement occurred in the first 6 months of treatment with gains of +12.5 (9.8, 15.2) letters in BRVO eyes and + 11.9 (6.4, 17.4) in CRVO eyes (Figure 6.1). Around 38% of eyes gained ≥ 15 letters (BRVO 36%, CRVO 41%). The proportion of eyes with VA > 70 letters increased from just over 20% in both groups at baseline to almost two-thirds in BRVO eyes (67%), but only one-third (33%) of CRVO eyes. CRVO eyes started with a mean VA more than 10 letters lower than the BRVO eyes (42.6 vs. 55.8 letters). The greatest crude gain in vision of +34.5 (23.3, 45.7) letters occurred in the 22 CRVO eyes with VA ≤20 letters at baseline, improving from count fingers (CF) or 3 (1.7) letters to 37.7 (26.3) letters. Three-line losses of vision occurred more in CRVO eyes (8 eyes, 11%) than BRVO eyes (3 eyes, 2%). Twenty-five eyes (11%) had a final VA ≤ 35 letters (6/60) after 12months (6 BRVO eyes, 19 CRVO eyes).

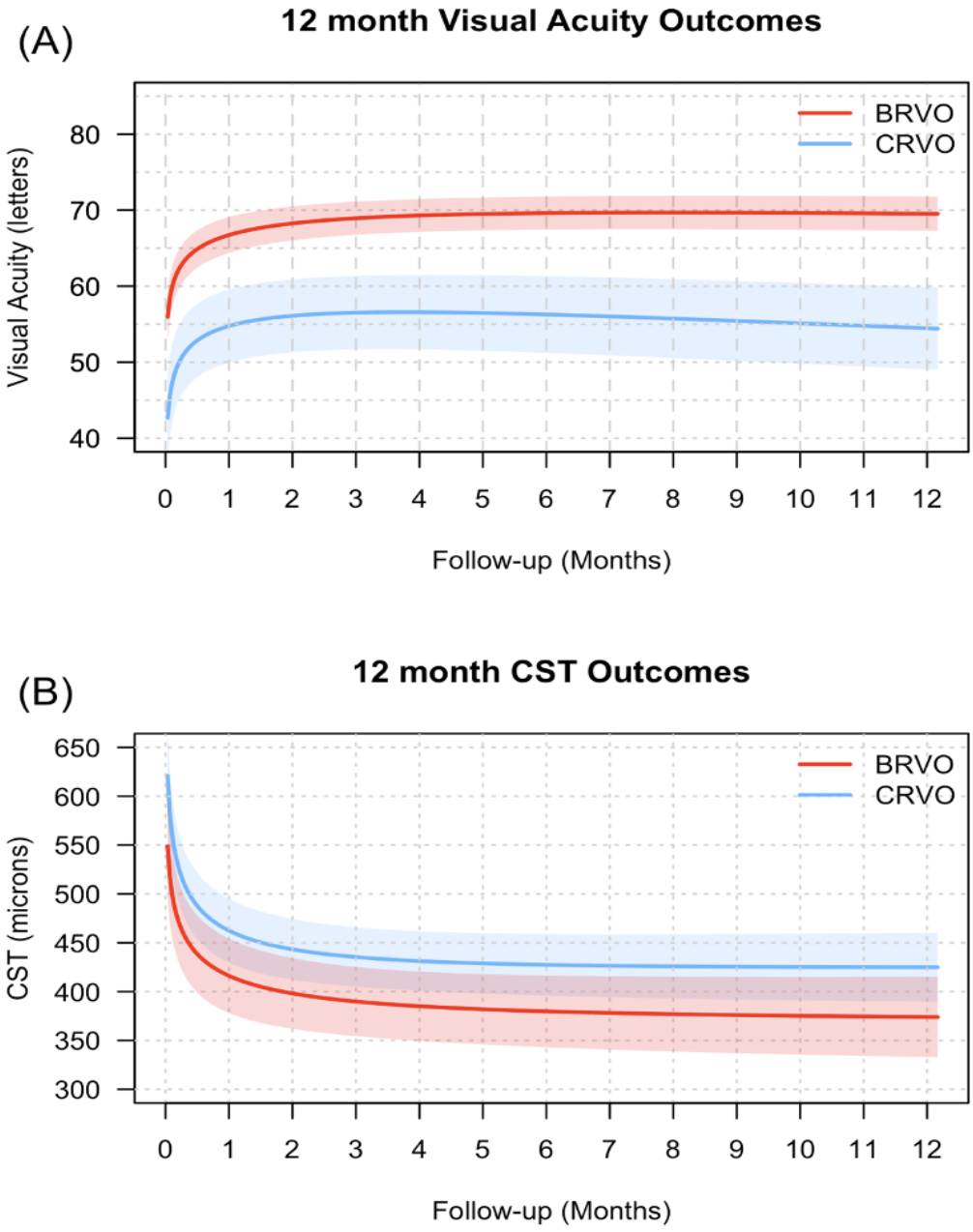
The crude mean (SD) changes in CST in BRVO of -155 (-190, -121) µm, and in CRVO of -198 (-252, -145) µm at 12 months (Figure 6.1, Table 6.2). Mean CST (SD) was higher in CRVO eyes than in BRVO eyes at baseline [627 (227) µm/511 (187) µm], at 6-months [453 (193) µm/387 (141) µm], and at 12-months [429 (198) µm/356 (109) µm], respectively. The CRVO eyes with VA ≤20 letters had the highest CST at baseline [730 (317) µm] and the greatest crude change in CST over 12 months of -298 (-438, -158) µm.

Table 6.2. Outcomes All eyes, BRVO, CRVO, CRVO (Baseline VA ≤ 20 and VA > 20 letters).

	All Eyes	BRVO	CRVO	CRVO VA ≤ 20 letters	CRVO VA > 20 letters
Eyes	220	135	85	21	64
VA, Baseline, mean (SD)	50.7 (22.8)	55.8 (18.6)	42.6 (26.4)	3.2 (1.7)	55.5 (15.5)
VA, 6 Months, mean (SD)	63.3 (20.2)	68.3 (15.4)	55.3 (24)	37.7 (26.3)	61.1 (20.3)
VA, 12 Months, mean (SD)	63.9 (21.1)	69.8 (15.4)	54.5 (25.3)	35.1 (26.7)	60.8 (21.4)
Δ VA, 6 Months, mean (CI)	12.6 (9.9,	12.5 (9.8, 15.2)	12.8 (7.3, 18.3)	34.5 (23.3, 45.7)	5.6 (0.3, 10.9)
Δ VA, 12 Months, mean (CI)	13.2 (10.4,	14 (11.1, 16.8)	11.9 (6.4, 17.4)	32 (20.6, 43.4)	5.3 (-0.1, 10.7)
Predicted Δ VA, 12 Months,		13.6 (11.3,	11.7 (9.0, 14.5)		
Gained 15 letters	38%	36%	41%	67%	33%
Lost 15 letters	5%	2%	11%	0%	14%
VA > 70 Baseline / 12 Months	21% / 54%	22% / 67%	20% / 33%	0% / 10%	27% / 41%
VA ≤ 35 Baseline / 12 Months	23% / 11%	14% / 4%	36% / 22%	100% / 52%	16% / 12%
CST, Baseline, mean (SD)	556 (211)	511 (187)	627 (227)	730 (317)	595 (182)
CST, 6 Months, mean (SD)	413 (166)	387 (141)	453 (193)	391 (187)	473 (192)
CST, 12 Months, mean (SD)	384 (154)	356 (109)	429 (198)	432 (273)	428 (170)
Δ CST, 6 Months, mean (CI)	-147 (-178, -	-130 (-164, -	-175 (-232, -	-345 (-480, -210)	-121 (-177, -65)
Δ CST, 12 Months, mean (CI)	-172 (-202, -	-155 (-190, -	-198 (-252, -	-298 (-438, -158)	-167 (-220, -113)
Predicted Δ CST, 12 Months,		-149 (-185, -	-196 (-231, -		
Completers n (%)	202 (92%)	125 (93%)	77 (91%)	18 (86%)	59 (92%)
Switchers n (%)	40 (18%)	26 (19%)	14 (16%)	5 (24%)	9 (14%)
Non-Completers n (%)	18 (8%)	10 (7%)	8 (9%)	3 (14%)	5 (8%)
Injections, median (Q1, Q3) *	7 (5, 9)	7 (5, 9)	7 (5, 9)	6 (5, 8)	7 (5, 10)
Visits, median (Q1, Q3) *	9 (7, 10)	8 (7, 10)	9 (7, 11)	9 (9, 11)	9 (7, 11)

n – Number, VA – Visual Acuity in letters, Δ – change from baseline**,** SD – Standard Deviation, CI – 95% Confidence Interval, CST – Central Subfield Thickness in microns, Q1 – First Quartile, Q3 – Third Quartile. All Eyes – Includes completers, switchers and non-completers. “Completers” – Eyes with 12 months of observation from the start of treatment, “Switchers” – Eyes receiving ≥ 2 injections of another treatment drug prior to completion of 12 months. Observations were included in the analysis only up to the first occurrence of switching agents. “Non-Completers” – Eyes not completing 12 months of observations from the start of treatment. * Last observation carried forward for switchers and non-completers. ¤ Predicted outcomes calculated from longitudinal generalised additive models.

Figure 6.1. 12-month Visual acuity and central subfield thickness outcomes treating BRVO and CRVO with bevacizumab therapy. Shading indicates confidence intervals surrounding mean predicted VA and CST.



6.4.3 Treatments and visits

BRVO completers (92%) had a median (Q1, Q3) of 7 (5,9) injections over 8 (7,10) visits, similar to CRVO completers (91%); 7 (5,9) injections and 9 (7,11) visits (Table 6.2). Mean injections given between 6 and 12 months was 2.4 in both BRVO and CRVO eyes. Thirty-

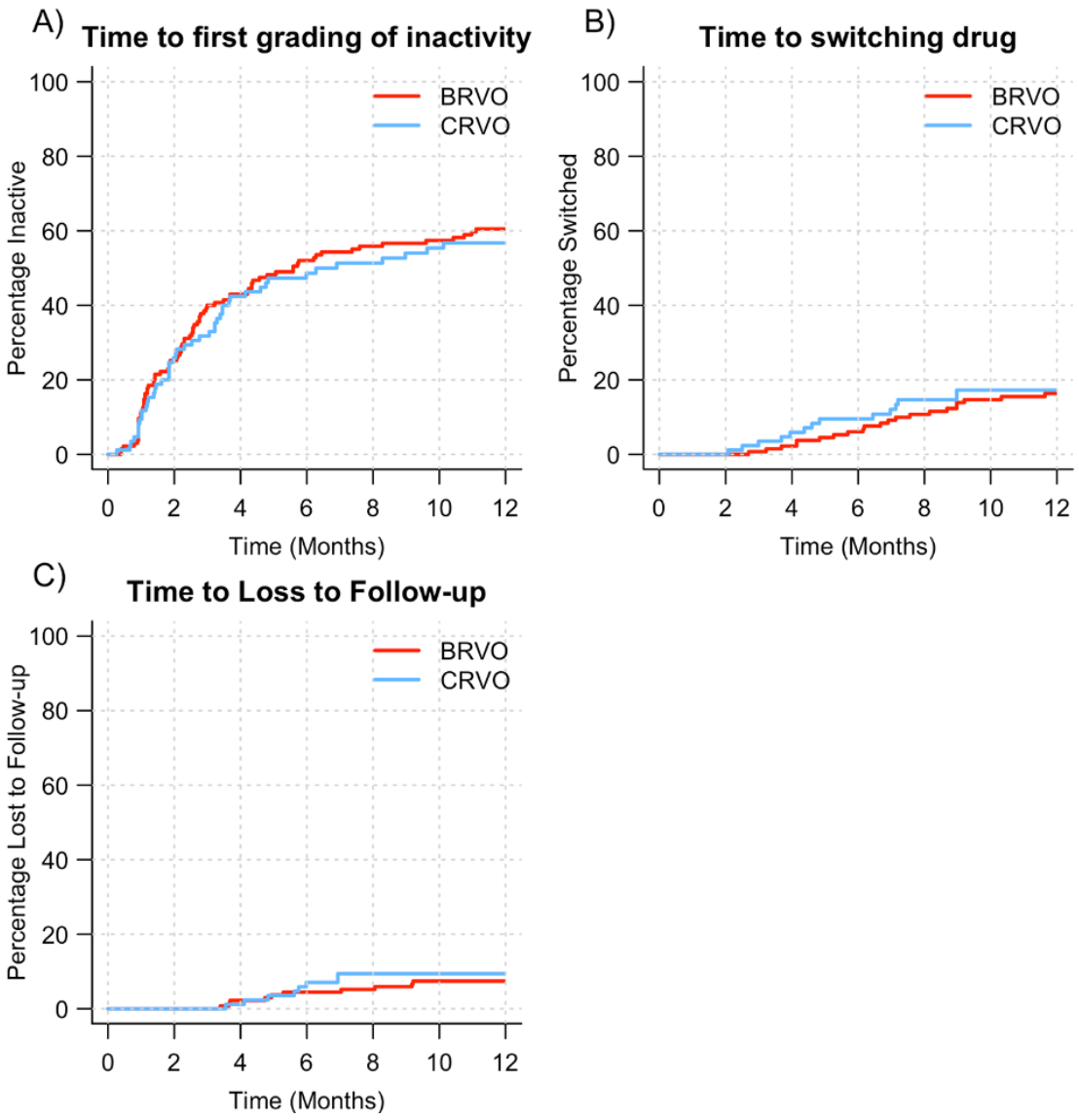
one eyes (14% of completers) had fewer than four injections with a median final VA of 71 letters. Macular laser at a median of 175 days was applied to 7 BRVO eyes (5%). Cataract surgery was performed in three eyes (2 BRVO and 1 CRVO).

6.4.4 Inactivity, switching and non-completion.

Kaplan–Meier survival curves, and log-rank tests demonstrated no difference in time to first grading of CMO inactivity between RVO types (P = 0.6), switching (P = 0.6) and non-completion (P = 0.6) for BRVO versus CRVO treated with bevacizumab over 12 months (Figure 6.2). Ninety-four BRVO eyes (69%) and 56 CRVO eyes (65%) recorded one or more visits with no CMO activity. The first grading of inactivity was at a median (Q1, Q3) of 84 (38, 191) days (Figure 6.2).

Forty eyes (18%) switched treatment within 12 months (Table 6.2). Switching occurred in 26 eyes BRVO (all in Australia) at a median (Q1, Q3) of 224 (163, 306) days and VA of 72 (63, 77) letters; aflibercept (11 eyes), IVTA/ Ozurdex (2 eyes) or to ranibizumab (13 eyes). Switching occurred in 14 CRVO eyes (13 in Australia) at a median (Q1, Q3) of 143 (114, 216) days and VA of 55 (40, 60) letters; aflibercept (7 eyes), IVTA (2 eyes), ranibizumab (5 eyes). The four eyes that switched to steroid had mean VA of 52 (51, 75) letters at 217 (126, 273) days when they switched. Eighteen eyes (10 BRVO and 8 CRVO) dropped out at a median time of 166 (130, 211) days with median VA of 75 (69, 79) letters.

Figure 6.2. Kaplan-Meier curve for A) first grading of inactivity, B) time to switching, and C) dropout by BRVO (red) or CRVO (blue).



6.4.5 Adverse events

Macular changes affecting vision were noted in 10 eyes at baseline (pigment clumping, atrophy, epiretinal membrane, macular hole) with a median VA at 12 months of 50 letters (6/24), including 2 of the 10 eyes that lost ≥ 15 letters, and 4 of the 25 eyes that had a final VA of ≤6/60. Pan retinal or sector photocoagulation was performed in 37 eyes (26 BRVO and 11 CRVO). Vitreous haemorrhage occurred in three eyes: all managed without vitrectomy. There was one reported case of non- infectious endophthalmitis with a baseline

VA of 11 letters and final VA of CF, but no traumatic cataract or retinal detachment from a total of 1507 injections.

6.5 Discussion

This analysis of prospectively collected observational data demonstrates that in a real-world setting, bevacizumab can be effective at improving vision in patients with MO secondary to RVO. The crude mean improvement in VA in eyes with BRVO and CRVO was 14.0 and 11.9 letters, respectively, with most of this improvement occurring in the first 6 months of treatment. These outcomes were achieved with a median of seven injections being administered for both BRVO and CRVO. Eyes with CRVO had a thicker mean CST at baseline (627 vs. 511 µm BRVO), but both groups achieved a significant improvement with treatment at 12 months (356 µm BRVO, 429 µm CRVO). Most BRVO and CRVO eyes experienced a significant improvement in vision regardless of the presenting VA.

A recent systematic review of RWS on the management of DMO and RVO-related MO indicated that visual and anatomical gains achieved often fall short of those achieved in RCTs, with suboptimal results likely stemming from reduced treatment frequency and differences in study population demographics and clinical parameters (Ang et al., 2020; Ciulla, Pollack, & Williams, 2021; Holekamp et al., 2018). The gains in VA and CST observed in our real-world BRVO cohort using bevacizumab were however only marginally inferior to those of the landmark RCTs which used ranibizumab and aflibercept (Table 6.3) (Brown et al., 2011; Clark et al., 2016; Tadayoni et al., 2017). Whilst we should be cautious in comparing study outcomes, the observation that 38% of eyes in our BRVO cohort were still active at any visit suggests a degree of undertreatment. This may explain the inferior results we report. The observation that only seven injections were delivered in the current study over 12-months, compared with the 8–10 injections delivered in RCTs further supports this hypothesis.

Table 6.3. Comparison of study results against RCTs and RWS for BRVO and CRVO

	Baseline VA (LogMAR letters)	12-month VA gain (LogMAR letters)	Total injections over 12-months
Our study results: BRVO	55.8	+14	7
BRAVO: Rbz (RCT) (Brown et al., 2011)	54.6	+18.3	8.5 (0.3mg)/8.4 (0.5mg)
VIBRANT: Afl (RCT) (Clark et al., 2016)	58.6	+17.1	9.0
BRIGHTER: Rbz (RCT) (Tadayoni et al., 2017)	59.5	+15.4	11.4 (24 months)
FRB!: Rbz/Afl (RWS) (Hunt et al., 2021)	55.6	+10.8 / +10.9	7
BERVOLT-BRVO: Bvz (RWS) (Kornhauser et al., 2016)	46.0	+13.0	7.6 (24 months)
OCEAN-BRVO:Rbz (RWS) (Callizo et al., 2019)	55.9	+13.1	4
Our study results: CRVO	42.6	+11.9	7
CRUISE (RCT) (Campochiaro et al., 2011)	48.3	+13.9	5.8 (0.3mg)/5.5 (0.5mg)
COPERNICUS (RCT) (Heier et al., 2014)	50.0	+16.2	8.7
CRYSTAL (Larsen et al., 2016)	53.0	+12.3	8.1
LEAVO: Rbz/Afl/Bvz (RCT) (Hykin et al., 2019)	54.1	+12.5 / +15.1 / +9.8 (100wks)	11.8/10.0/11.5
FRB!: Rbz/Afl (RWS) (Niedzwiecki et al., 2022)	36.9/42.5	+9.8 / +16.6	7
BERVOLT-CRVO: Bvz (RWS) (Brown et al., 2011)	28.0	-4.0	9.6 (24 months)
OCEAN-CRVO:Rbz (RWS) (Brown et al., 2010)	43.9	+4.1	5

Abbreviations: Afl, aflibercept; Bvz, bevacizumab; Rbz, ranibizumab; RCTs, randomised controlled trials; RWS, real-world setting.

The improvement in VA in eyes with BRVO achieved in this current study is similar to those reported by other RWS which achieved a similar treatment frequency, irrespective of which anti-VEGF agent was used (Callizo et al., 2019; Kornhauser et al., 2016). These data suggest that, at least for BRVO, the choice of anti-VEGF used may have less influence on treatment outcomes than the frequency of treatment. This hypothesis is supported by the recent analysis of eyes with BRVO in the FRB! registry which were treated with either ranibizumab or aflibercept (Hunt et al., 2021). The mean change in VA from a similar mean baseline in this RWS (+10.9 letters) was comparable to that observed in the current study

with a similar number of injections having been administered (median also seven). Similarly, the mean CST improvement for BRVO eyes in our study of -149 µm was within the range reported in the cohorts treated with aflibercept (-170 µm) or ranibizumab (-147 µm).

CRVO is regarded as a separate, more severe disease entity than BRVO with generally worse patient outcomes. Compared with both CRUISE and COPERNICUS (Table 6.3) (Campochiaro et al., 2011; Heier et al., 2014), eyes with MO secondary CRVO in the current study recorded inferior improvements in VA, (11.9 vs. 13.9 and 16.2 letters, respectively), despite presenting with worse vision. CST at baseline was comparable between CRUISE [689 µm (0.5 mg)], COPERNICUS (662 µm) and our study cohort (627 µm), but eyes in the current study had less improvement in CST (-198 µm) at 12 months compared with that observed in both CRUISE and COPERNICUS (-462 vs. -413 µm). As 54% of eyes in the current study were active at every visit it is again likely that undertreatment explains the poorer VA and CST results in our CRVO cohort compared with the landmark RCTs as both CRUISE and COPERNICUS had prescriptive treatment regimens which delivered more injections compared to the current study (9.3, 8.7 vs. 7). The mean VA gain in CRYSTAL, which delivered fewer treatments than did CRUISE (mean treatments 8.1 vs. 9.3), was 12.3 letters (Larsen et al., 2016), similar to the present study. However, patients enrolled in CRYSTAL had a significantly higher baseline mean VA than those in our cohort with CRVO, which may have imposed a ceiling effect on their potential gains. That they achieved a significantly greater reduction in mean CST of -335.6 µm, compared with -198 µm observed in our CRVO patients, suggests this may be the case (Larsen et al., 2016).

The results from our CRVO cohort are better than those reported by other RWS. The CRVO cohort of BERVOLT actually reported a decrease in VA at 12 months, whilst CRVO eyes in OCEAN only achieved +4.1 letters over a 1-year period (Callizo et al., 2019; Kornhauser et al., 2016). Undertreatment likely explains the disappointing results of these other RWS. Whereas eyes in BERVOLT received only 7.6 injections over 24 months and those in

OCEAN received a median of just 5 (Callizo et al., 2019; Kornhauser et al., 2016), eyes with CRVO in the current study received a median of seven injections in 12 months with correspondingly better visual outcomes, thereby demonstrating that an adequate number of injections can be given to eyes with CRVO in routine clinical practice.

Whilst it is again very likely that the primary determinant of treatment outcomes in CRVO is treatment frequency, differences between the efficacy of the three VEGF inhibitors may also be important. LEAVO reported an improvement in BCVA of +12.5 for ranibizumab for CRVO, +15.1 for aflibercept compared to just +9.8 letters for bevacizumab (Hykin et al., 2019). The authors concluded that, when adjusted for all other factors, bevacizumab was not non-inferior to aflibercept. Data recently published from the FRB! registry reported that eyes with CRVO treated with aflibercept (16.6 letters) had significantly greater 12-month visual gains than eyes treated with than ranibizumab (9.8) (Table 6.3) (Niedzwiecki et al., 2022). This compares with the observed mean VA gain of 11.9 letters in eyes treated with bevacizumab in the current study. Whilst direct comparison is not possible, these data suggest that, unlike BRVO, the choice of anti-VEGF also may also influence the treatment outcome for patients presenting with MO secondary to CRVO. Further studies comparing bevacizumab to ranibizumab and aflibercept in a real-world setting would be helpful.

Approximately 20% of eyes in both the BRVO and CRVO cohorts switched agents over the course of the study and in most cases, this was to another VEGF inhibitor. Most switchers were in the Australian cohort. As the decision to switch agents is at the clinicians' discretion and this decision is not documented in FRB! we cannot determine if switching was a result of a poor response to bevacizumab or due to changes in how the Australian Federal government reimbursed anti-VEGF treatments starting in 2016. The observation that the mean VA at time of switching in BRVO was 72 letters nevertheless suggests that individuals with BRVO were switched for reasons other than treatment efficacy. No conclusion can be drawn from the CRVO cohort as the mean VA at time of switching in CRVO was lower at 55

letters. The change in funding could also have affected the clinicians' choice of agent when commencing treatment as aflibercept and ranibizumab were subsidised only if the presenting vision was > 20 letters for BRVO or > 24 letters for CRVO. Australia contributed 67% of all eyes in the analysis that commenced bevacizumab treatment before January 2016 but only 23% of CRVO eyes and 30% of BRVO eyes after January 2016. The median (Q1, Q3) baseline VA and CST in Australian CRVO eyes was worse after January 2016 dropping from 43 (23, 58) letters and 585 µm to 33 (3, 45) letters and 845 µm. This suggests that many eyes in the Australian cohort commenced on bevacizumab after 2016 were those with worse CRVOs which did not fulfil the funding criteria for other anti-VEGF agents. This raises the possibility that there is a selection bias in our CRVO cohort with those patients with ischaemic CRVO being overrepresented. It is unlikely that a similar bias was present in the BRVO cohort as the baseline characteristics of BRVO eyes in Australia were not different before and after 2016.

This study used observational data from a real-world database so there are the usual limitations that apply to RWS. Clinical judgement and patient preferences would influence the decision-making process. However, adherence to treatment in this cohort was excellent with 93% of individuals with BRVO and 89% of those with CRVO completing 12 months.

In conclusion, our study found that bevacizumab can achieve good visual outcomes for both BRVO and CRVO in a real-world setting which are only slightly inferior to those reported by the landmark RCTs of ranibizumab and aflibercept. This is most likely due to less aggressive treatment resulting in suboptimal reductions in CST. Our findings were, however, generally better than those of other RWS, which tended to treat less aggressively (Callizo et al., 2019; Kornhauser et al., 2016).

Although a detailed cost analysis comparing the efficacy of the various anti-VEGFs agents for treating RVO is beyond the scope of the current study, our findings support the first-line use of bevacizumab for RVO in health economies with limited financial resources.

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CHAPTER 7: 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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7.2 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 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 (-231µm) was similar to CRVO (-259µm; P = 0.33) but greater than BRVO eyes (-151µm; P = 0.003). The groups had similar median burdens of 8 injections and 9 visits.

Conclusions: HRVO generally experienced the greatest mean change in VA of the 3 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.

7.3 Introduction

Hemi-retinal vein occlusion (HRVO) is regarded pathologically as a type of central retinal vein occlusion (CRVO) with a better prognosis (Chopdar, 1982, 1984; Hayreh & Hayreh, 1980). For many years it was managed like branch retinal vein occlusion (BRVO) with laser (BVOS_group, 1984). 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 (+8.8 letters), followed by BRVO (+4.5 letters) and CRVO (-1.4 letters) (I. U. Scott et al., 2012).

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 (I. U. Scott et al., 2017). 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) (Boyer et al., 2012; Campochiaro et al., 2015; Campochiaro et al., 2010; Korobelnik et al., 2014; Shalchi, Mahroo, Bunce, & Mitry, 2020). Just last year (2020) Vader et al. reported non-inferiority of bevacizumab and ranibizumab in RVO with a sub-group analysis that combined 47 HRVO eyes with 97 CRVO eyes (Vader et al., 2020). To support that choice the authors cited a review article which argued HRVO was a variant of CRVO, with similar pathogenesis and risk factors (Karia, 2010).

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.

7.4 Materials And Methods

7.4.1 Design and setting

This study adhered to the tenets of the Declaration of Helsinki and followed the STROBE checklists for Strengthening the Reporting of Observational Studies in Epidemiology (von Elm et al., 2008). Data were obtained from the prospectively designed Fight Retinal Blindness! RVO module of the Save Sight Registries.

Ethics approval was obtained in Australia and New Zealand, Ireland, Spain, Slovakia, Italy and France for eyes included in this study from the Royal Australian and New Zealand College of Ophthalmologists and the University of Sydney Human Research Ethics Committees (HREC#16.09), Institutional Review Boards of the Mater Private Hospital (1/378/2130) in Dublin, the Hospital Clinic of Barcelona, Spain (2015/57-OFT-HUSC) , Etická komisia UN- Nemocnica svätého Michala, a.s., Bratislava, Slovakia, the IRCCS Cà Granda Foundation Maggiore Policlinico Hospital Milan and the Société Française d'Ophtalmologie (2017_CLER-IRB_II-05) respectively. All patients gave their informed consent.

7.4.2 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 categorized 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 (log MAR) visual acuity chart (VA; 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.

7.4.3 Patient selection

We studied treatment-naïve patients with CMO due to HRVO commencing therapy with either aflibercept (2mg Eylea, Bayer), bevacizumab (1.25 mg Avastin; Genentech, Inc., CA, USA/Roche, Basel, Switzerland) or ranibizumab (0.5mg Lucentis, Genentech Inc/Novartis) between 1st January 2010 and 1st 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.

7.4.4 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.

7.4.5 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, standard deviation (SD), median, first and third quartiles (Q1, Q3) and percentages where appropriate. Comparison between cases and controls used t-tests, Wilcoxon rank sum tests, Chi-square tests and Fisher's exact tests where appropriate. Crude visual and anatomic outcomes used the last observation carried forward (LOCF) 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 version 4.1.0 (cran.r-project.org) utilising the *lme4* (1.1-27.1) and *mgcv* (V1.8-35) packages for linear and generalised additive mixed effects models respectively (R Core Team, 2020). The *survival* (3.2-11) package was used to generate the Kaplan-Meier estimates (R Core Team, 2020). A P-value < 0.05 was considered statistically significant.

7.5 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.

7.5.1 Demographic characteristics

Baseline demographic characteristics are presented in Table 7.1. 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 (482μm; P = 0.004) and significantly less than that of the CRVO eyes (630μm; 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 = 0.007). The proportion of eyes starting treatment on each VEGF inhibitor was similar.

Table 7.1. Demographic characteristics with significant differences between HRVO vs. BRVO and HRVO vs. 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

HRVO – hemiretinal vein occlusion, BRVO – branch retinal vein occlusion, CRVO – central retinal vein occlusion, n – Number, VA – visual acuity in letters read on a logarithm of minimum angle of resolution chart, SD – Standard Deviation, CST – central subfield thickness in microns. P-values reflect comparison of HRVO vs. BRVO or comparison of HRVO vs. CRVO.

7.5.2 Visual outcomes at 6 and 12 months

Visual acuity in HRVO eyes started closer to the CRVO eyes but soon resembled that of the BRVO eyes once treatment began (Tables 7.1, 7.2 and Figure 7.1A). 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).

Table 7.2. 6-month and 12-month outcomes in eyes with HRVO, compared to eyes with BRVO or CRVO. Significant differences between HRVO vs. BRVO and HRVO vs. CRVO are in bold (P < 0.05).

	HRVO	BRVO	P-value (vs. HRVO)	CRVO	P-value (vs. HRVO)
Eyes, n	79	590		344	
Visual Acuity (letters)					
VA Baseline, mean (SD)	53.8 (17.7)	59.4 (14.9)	0.009	51.9 (18.7)	0.40
VA 6m, mean (SD)	69.9 (13.7)	69.8 (14)	0.96	60.7 (21.6)	**< 0.001**
VA 12m, mean (SD)	70.2 (15.3)	70.8 (14)	0.74	60.4 (23)	**< 0.001**
Change in VA (letters)					
ΔVA 6m, mean (95% CI)	16.1 (12.6,	10.4 (9.3, 11.5)	0.003	8.8 (6.6, 11.1)	**< 0.001**
ΔVA 12m, mean (95% CI)	16.4 (13.1,	11.4 (10.2,	0.006	8.5 (6.1, 10.9)	**< 0.001**
Adjusted ΔVA 12m, mean	15.6 (11.9,	13.2 (11.1,	0.19	5.9 (3.6, 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 / 12m, %	24% / 68%	32% / 68%	0.15 / 1.0	21% / 45%	0.54 /**< 0.001**
≤ 35 letters, Baseline / 12m, %	20% / 3%	9% / 3%	**0.007** /1.0	22% / 16%	0.88 /**< 0.001**
Central Subfield Thickness					
CST Baseline, mean (SD)	550 (186)	482 (159)	0.004	630 (223)	**0.002**
CST 6m, mean (SD)	332 (112)	342 (115)	0.45	402 (213)	**< 0.001**
CST 12m, mean (SD)	319 (124)	330 (105)	0.31	371 (181)	**0.001**
Change in CST (µm)					
Δ CST 6m, mean (95% CI)	-214 (-257, -	-141 (-154, -	0.003	-229 (-258, -	0.60
Δ CST 12m, mean (95% CI)	-231 (-277, -	-151 (-166, -	0.003	-259 (-287, -	0.33
Adjusted Δ CST 12m, mean	-218 (-253, -	-204 (-224, -	0.42	-173 (-195, -	**0.019**

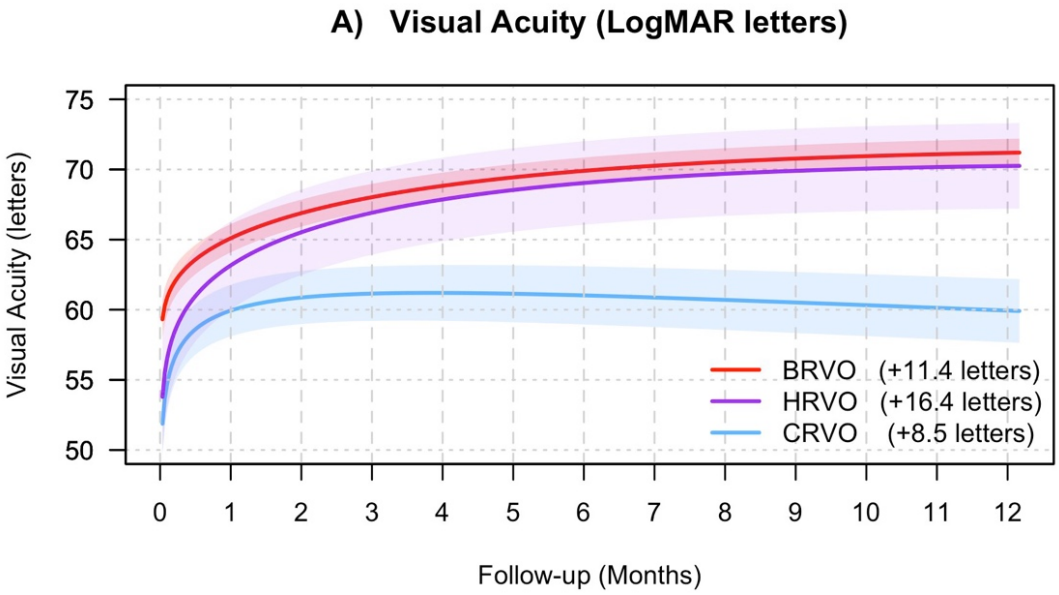
Treatment and Visits					
Injections, median (Q1, Q3) [a]	8 (6, 10)	8 (5, 9)	1.0	8 (5, 10)	1.0
Visits, median (Q1, Q3) [a]	9 (9, 11)	10 (8, 12)	0.38	11 (8, 13)	0.12
Suspension of treatment, n (%)	12 (15%)	96 (16%)	1.0	41 (12%)	0.45
Never became inactive in 12m,	12 (15%)	174 (29%)	0.007	85 (25%)	0.07
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 12m, n (%)	9 (11%)	100 (17%)	0.26	58 (17%)	0.30

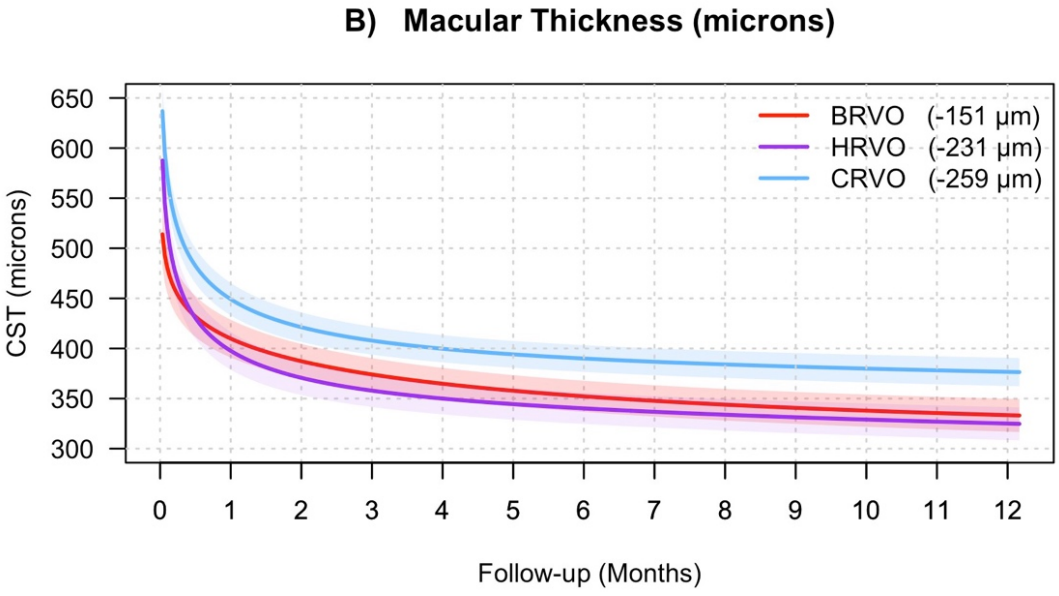
n – Number, 6m – 6 months, 12m – 12 months, Δ – change from baseline, SD – Standard Deviation, CI – 95% Confidence Interval, µm - microns, Adjusted – using analysis of covariance (ANCOVA) controlling for first treatment age and baseline VA or CST as fixed effects and nesting within patients (both eyes) or the same practice as random effects, Q1 – First Quartile, Q3 – Third Quartile. [a] Calculated only in completers receiving VEGF monotherapy throughout with Generalised Poisson models used to generate P-values. [b] Periods >180 days containing recorded visits and no treatment.

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 (I. U. Scott et al., 2017). 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 sub-type, we explored the effect of controlling for them using analysis of covariance (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; $P < 0.001$).

Figure 7.1. 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% confidence intervals. The legend has the 12-month Mean Changes from baseline in VA and CST in parentheses.





7.5.3 Macular thickness

The mean CST in HRVO eyes approached that of the BRVO controls very soon after treatment commenced (Figure 7.1B). This was achieved with a significantly greater mean change in CST in HRVO eyes compared to BRVO controls at 6 months (-214μm vs. -

141μm; P = 0.003) and at 12 months (-231μm vs. -151μm; P = 0.003). The HRVO and BRVO groups had very similar mean final CST (319μm vs. 330μm; P = 0.31). After controlling for baseline CST, the adjusted CST change in HRVO and BRVO were similar (P = 0.42, Table 7.2).

The mean CST at baseline was lower in HRVO eyes compared to CRVO eyes (550μm vs. 630μm; P = 0.002). The separation continued to 12 months (319μm vs. 371μm; P = 0.001). The mean change in CST was highest in the CRVO group (-259μm) 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 7.2).

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

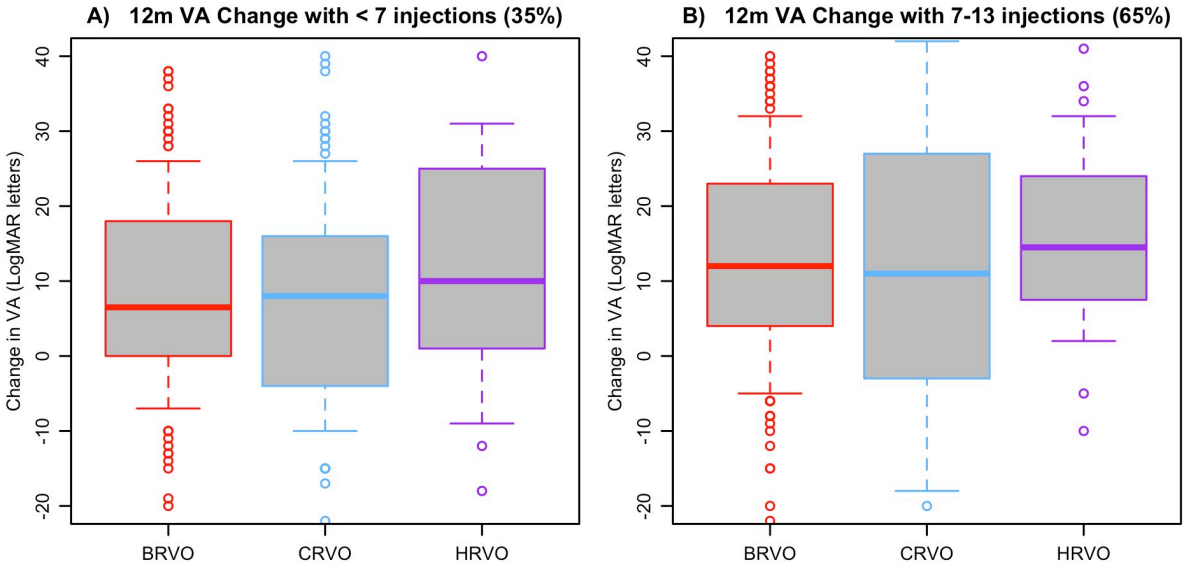
7.5.4 Treatments and visits

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 7.2). 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) (Brown et al., 2011; Brown et al., 2013; Campochiaro et al., 2011; Clark et al., 2016). 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.

Figure 7.2. 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 interquartile range.



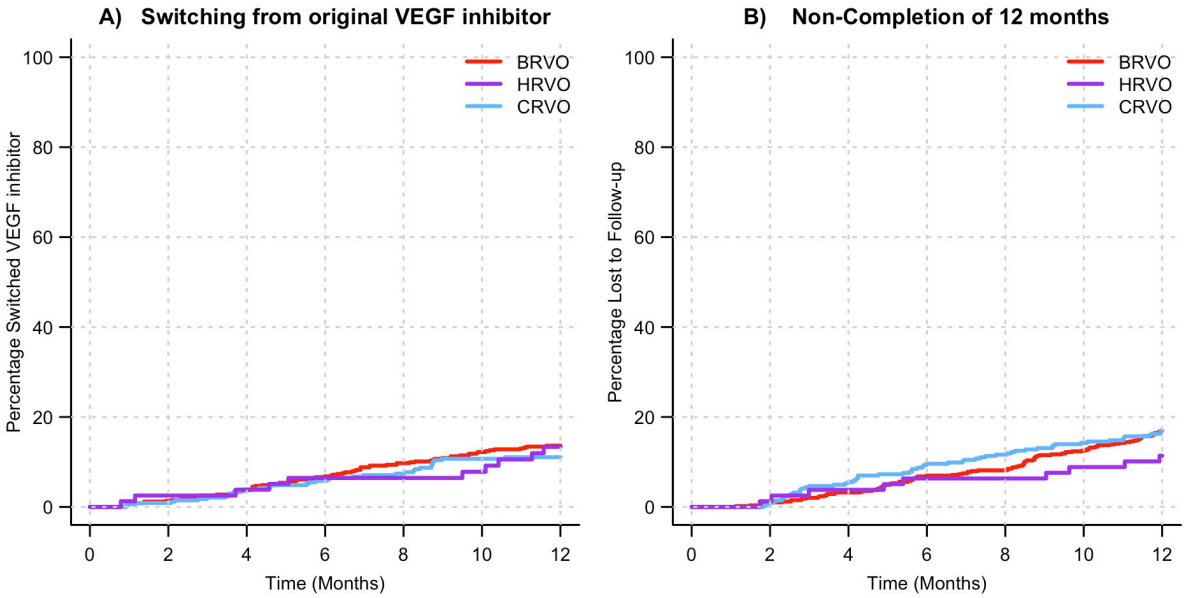
7.5.5 Switching and Dropout

Switching VEGF inhibitors occurred in 11 HRVO eyes (14%) which was most commonly to aflibercept (6 eyes) and from bevacizumab (5 eyes) with very similar switching patterns in the control groups (Figure 7.3). 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 to 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 7.3), with mean final VA of 80 (69, 84) letters, mean VA change from baseline of +25 (17, 41) letters and mean final CST of 275μm (265, 281). Some eyes may have completed successful

treatment. Documented reasons for loss to follow-up included one patient going to another doctor and two declining further treatment.

Figure 7.3. Kaplan-Meier survival curves describing time to A) switching from original VEGF inhibitor and B) non-completion by RVO type.



7.5.6 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 twenty-three 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.

7.6 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. Visual acuity 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 (I. U. Scott et al., 2012). 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 8 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, i.e., 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 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, -345μm) (Campochiaro et al., 2010). The VIBRANT study also included eyes with HRVO without reporting the proportion (+17 letters, -280μm) (Campochiaro et al., 2015). 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 -170μm) were less impressive than those pivotal RCTs (Hunt et al., 2021). 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 -200μm), a smaller RCT comparing bevacizumab and ranibizumab in eyes with BRVO excluded eyes with HRVO (Narayanan et al., 2016).

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 (Vader et al., 2020). The six-month visual gains were surprisingly high (+16 to +17 letters) while CST changes were modest (-330 to -400μm) 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 -460μm) (Brown et al., 2010).

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, randomization distributed 24 HRVO eyes to the aflibercept group (13%) and 31 eyes to the bevacizumab group (17%) in the SCORE2 study (I. U. M. D. M. P. H. Scott et al., 2016). Another comparative study had 15% HRVO in a ranibizumab group and 19% in a bevacizumab group when it compared outcomes in CRVO (Vader et al., 2020).

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 fulfill 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 to 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 7 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 (Green, Chan, Hutchins, & Terry, 1981). 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 (Chopdar, 1982). This may allow development of a third collateral process in

HRVO anterior to the lamina cribrosa to the unobstructed second venous trunk which is hemodynamically significant (McAllister & Barry, 1991).

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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CHAPTER 8: CENTRAL RETINAL VEIN OCCLUSION 36-MONTH OUTCOMES WITH ANTI-VASCULAR ENDOTHELIAL GROWTH FACTORS: THE FIGHT RETINAL BLINDNESS! REGISTRY

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8.1 Abstract

Purpose: To analyse the 3-year outcomes in a broad population of patients starting vascular endothelial growth factor (VEGF) inhibitors for central retinal vein occlusion (CRVO) in routine clinical practice.

Design: Observational database study

Participants: 527 treatment-naïve CRVO eyes that commenced VEGF inhibitors between December 1, 2010-2018 tracked in the Fight Retinal Blindness! registry.

Methods: Longitudinal models were used to plot changes in visual acuity (VA) and central subfield thickness (CST).

Main outcomes measures: Mean change in VA from baseline to 36 months, injections, visits, completion, switching and suspensions of therapy > 180 days at final review.

Results: Overall (527 eyes) mean VA change (95% CI) was +10 (7, 12) letters, 37% had final VA ≥ 70 and 30% ≤ 35 letters, mean CST changed -306µm. Completers (257/527, 49%) had mean 36-month changes in VA and CST of +12 letters and -324µm with a median of 18 injections at 26 visits. The adjusted mean VA change was similar with each VEGF inhibitor (mean, +11.4 letters) despite a greater reduction in CST with aflibercept (-310µm) vs. ranibizumab (-258µm) vs. bevacizumab (-216µm; $P < 0.001$). Eyes with baseline VA that was trial-eligible (19-73 letters, 356/527, 68%) gained 7 letters, very-poor (< 19 letters, 129/527, 24%) gained 22 letters, or very-good (> 73 letters, 42/527, 8%) lost 7 letters. Switching (160/527, 30%) was most often to aflibercept (79 eyes). Using suspensions and discontinuation reasons we identified similar proportions had ceased therapy (154/527, 29%) as were still receiving it at 36 months (165/527, 31%). Only 62/527 eyes (12%) had resolution of macular oedema without treatment for over 6 months.

Conclusions: Patients with CRVO that commenced VEGF inhibitors in routine care for whom follow-up was available had VA improvements of around 12 letters at three years, but with more than 50% lost to follow the VA outcome for the entire group is likely worse. The choice of VEGF inhibitor influenced CST but not VA outcomes. We estimate that around half of eyes were still receiving injections after 36 months.

8.2 Introduction

Vascular endothelial growth factor (VEGF) inhibitors are recommended as first line treatment of cystoid macular oedema (CME) due to central retinal vein occlusion (CRVO) (Flaxel et al., 2020; Schmidt-Erfurth et al., 2019). This is based on the overwhelming safety and efficacy of ranibizumab and aflibercept reported in pivotal randomized clinical trials (RCT) (Boyer et al., 2012; Braithwaite, Nanji, Lindsley, & Greenberg, 2014; Brown et al., 2013; Campochiaro et al., 2011; Heier et al., 2014; Korobelnik et al., 2014; Larsen et al., 2018). Bevacizumab is an "off-label" alternative VEGF inhibitor listed on the World Health Organization list of essential medicines with similar outcomes to approved agents when compared by RCTs at 2 years (Hykin et al., 2019; Scott et al., 2019; "World Health Organization Model List of Essential Medicines, 21st List.," 2019). Outcomes beyond 2 years are less clear as there are few patients enrolled in extension studies that followed the RCTs. This is where real-world evidence (RWE) can help but few studies have significant follow-up.

Existing evidence fails to account for many patients with CRVO that may experience disease resolution or that abandon therapy within a few years of starting it. A large RWE study extracted measurements from the medical records of 3577 patients with CRVO treated with VEGF inhibitors in the United Kingdom but had visual acuity in only 6% of eyes at 3 years (Gale et al., 2020). Smaller retrospective studies often avoid the problem of variable follow-up by performing "completers only analyses" only studying eyes with a requisite period of observation such as 3 or 5 years (Chatziralli et al., 2018; Spooner, Fraser-Bell, Hong, & Chang, 2019; Wu et al., 2022).

Few eyes participated in long-term extension studies that followed pivotal randomized controlled trials (RCT). The RETAIN study (macular oedema due to b*R*anch r*ET*inal vein occlusion or centr*A*l retinal ve*I*n occlusio*N* previously treated with intravitreal ranibizumab) is often cited in discussions regarding long-term outcomes of VEGF therapy in CRVO

(Campochiaro et al., 2014). It concluded that around half of eyes still required treatment at 4 years. The sample enrolled in the RETAIN extension study consisted of 8% of participants from CRUISE (Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study) but was found to be representative of the original cohort (Brown et al., 2010).

Our objective was to study 3-year outcomes in a broad population of patients starting VEGF inhibitors for CRVO in routine care – with particular interest in visual outcomes, number of injections and need for ongoing treatment – by analysing data from the Retinal Vein Occlusion module of the Fight Retinal Blindness! registry.

8.3 Materials And Methods

8.3.1 Design and setting

This was a retrospective observational study using anonymized data obtained from the Retinal Vein Occlusion module of the Fight Retinal Blindness! registry (Gillies et al., 2014). Treatment decisions were made at the discretion of the physician and patient during routine clinical practice. Data points were numeric, drop-down lists or mutually exclusive. These included visual acuity (VA) in letters (best of uncorrected, corrected or pinhole) using a logarithm of the minimum angle of resolution (log MAR) chart, central subfield thickness (CST [μm]) assessed with optical coherence tomography (OCT) using the same machine for the same patient throughout, treatments given and adverse events. The baseline visit, defined by the first injection, required entry of additional data regarding demographics, the type of RVO (Central, Branch or Hemi-retinal) and presence of key risk factors.

Ethics and data protection approval was granted in: Australia and New Zealand - Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09); United Kingdom -

Caldicott Guardian (Until Sept 2024); Ireland - Mater Private Hospital (IRB, 1/378/2130); Spain - Comité Etico de Investigación Medica, Hospital Clínic de Barcelona (2015/57-OFT-HUSC); Italy - IRCCS Cà Granda Foundation Maggiore Policlinico Hospital; France - Société Française d'Ophtalmologie (2017_CLER-IRB_II-05). Patients gave their informed consent, which was "opt-in" in European centers and "opt-out" in Australia and New Zealand, as approved by local ethics committees. Due to the non-interventional nature of the registry, the Medical Ethics Committees in Italy and the Netherlands ruled that approval was not required for this study. The study adhered to the tenets of the Declaration of Helsinki and strobe checklists for reporting observational studies (von Elm et al., 2008).

8.3.2 Patient Selection and Definitions

We included treatment-naïve patients with CME due to CRVO that commenced treatment with either bevacizumab (1.25 mg Avastin; Genentech, Inc., CA, USA/Roche, Basel, Switzerland), ranibizumab (0.5mg Lucentis, Genentech Inc/Novartis) or aflibercept (2mg Eylea, Bayer) between 1st December 2010 and 1st December 2018. Branch and hemi-retinal vein occlusions were excluded. The study period included the first treatment visit until the 36-month visit closest to 1095 days +/- 30 days. "Completers" were defined as having follow-up ≥ 1065 days. Treatment during the 3-year study was either "Monotherapy" with the original VEGF, "VEGF-Switched" (≥ 2 alternate VEGF injections) or "Steroid-Switched" (≥ 1 steroid injection). "Suspension" of therapy was defined as a period of observation that contained one or more visits without therapy spanning > 180 days, either concluding at final review or with resumption of therapy within the 3-year study.

8.3.3 Outcomes

The primary outcome was the mean change in VA from baseline to 36 months. Secondary outcomes included percentage of eyes with final VA ≥ 70, VA ≤ 35 letters, VA gain or loss ≥ 15 letters; mean change in CST; frequency of visits and injections; suspensions of therapy;

non-completion; switching and adverse events. The FRB! project collects a prospectively defined, minimum, patient-centred outcomes set with mandatory fields, so all data analysed were 100% complete and within pre-specified ranges.

8.3.4 Statistical analysis

Data were summarized where appropriate with counts, percentages, means, standard deviations (SD), 95% confidence intervals (CI), medians and first and third quartiles (Q1, Q3). Since we observed high rates of switching and non-completion, we considered it inappropriate to compare VEGF agents based on unadjusted outcomes in the select eyes that were monotherapy completers. Instead, we used generalized additive mixed effects models (GAMMs) to predict VA and CST outcomes with VEGF inhibitors combined (censoring if “Steroid-Switched”), separately we compared response to individual VEGF inhibitors (censoring if “VEGF-Switched” or “Steroid-Switched”), adjusting for baseline age, baseline VA (or CST) as fixed effects, nesting of outcomes within practice and eyes from the same patient were considered random effects.

Unadjusted outcomes were reported without censoring after switching with grouping by treatment received (Monotherapy, VEGF-Switched or Steroid-Switched) using last observation carried forward in non-completers. Supplementary analyses included outcomes in switchers and by baseline VA according to the inclusion criteria of major trials (Brown et al., 2010; Brown et al., 2013; Hykin et al., 2019; Korobelnik et al., 2014; Larsen et al., 2018; Scott et al., 2017) (*very-poor* < 19 letters, *trial-eligible* 19-73 letters or *very-good* > 73 letters). Kaplan-Meier survival curves were generated for switching and non-completion with the drugs compared using Cox-proportional hazards models.

Statistical analysis was performed using R version 4.1.3 (http://www.R-project.org/) utilising the *mgcv* (V1.8-35) and *itsadug* (V2.4) packages for generalized additive mixed effects

models, the *survival* (3.3-1) package to generate the Kaplan-Meier estimates and *coxme* (2.2-16) for comparing event based outcomes by drug (R Core Team, 2020).

8.4 Results

8.4.1 Patient Characteristics and Disposition

We identified 527 treatment naïve eyes with CME due to CRVO that started VEGF inhibitors between December 1, 2010, and December 1, 2018 (Table 8.1). Baseline mean (SD) age was 71 years (12), mean VA was 41 letters (25), and mean CST was 641 μm (233) overall. Demographics were broadly similar between groups whether stratified by initial VEGF inhibitor (128 [24%] bevacizumab, 227 [43%] ranibizumab or 172 [33%] aflibercept) or by the treatment received over 3 years (366 [68%] monotherapy, 98 [19%] VEGF-switched and 63 [12%] steroid-switched) (Tables 8.2 and 8.3). Baseline characteristics of eyes that completed 36-months follow-up (257 [49%]) or non-completed 36 months (270 eyes [51%]) are described in (Table 8.4).

Table 8.1. Baseline Demographic Characteristics of Patients Included in the Study

Eyes, n	527
Patients, n	516
Initial VEGF inhibitor:	
Bevacizumab, n (%)	128 (24%)
Ranibizumab, n (%)	227 (43%)
Aflibercept, n (%)	172 (33%)
Female, % patients	42%
Age, mean (SD)	71 (12)
VA, mean (SD) letters	41 (25)
Very-poor VA < 19 letters, n (%)	129 (24%)
Trial-eligible VA 19-73 letters, n (%) *	356 (68%)
Very-good VA > 73 letters, n (%)	42 (8%)
CST, mean (SD), μm	641 (233)
Pseudophakia, %	21%
Hypertension, %	61%
Glaucoma, %	16%

n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness, VEGF – vascular endothelial growth factor inhibitors including. * Stratification by baseline VA based on inclusion criteria of major trials (typically 19-73 letters).(Brown et al., 2010; Brown et al., 2013; Hykin et al., 2019; Korobelnik et al., 2014; Larsen et al., 2018; Scott et al., 2017)

Table 8.2. Baseline Demographic Characteristics by Initial treatment

	All Eyes	Bevacizumab	Ranibizumab	Aflibercept	P-value
Eyes, n	527	128	227	172	
Initial VEGF inhibitor:					
Bevacizumab, %	24%	100%			
Ranibizumab, %	43%		100%		
Aflibercept, %	33%			100%	
Female, % patients	42%	36%	43%	45%	0.25
Age, mean (SD)	71 (12)	69 (13)	72 (12)	72 (12)	0.13
VA, mean (SD)	41 (25)	42 (26)	39 (25)	43 (25)	0.35
VA < 19 letters	24%	25%	26%	23%	0.79
VA 19-73 letters *	68%	65%	67%	71%	0.48
VA > 73 letters	8%	10%	8%	6%	0.49
CST, mean (SD)	641 (233)	640 (224)	655 (242)	624 (228)	0.44
Pseudophakia, %	21%	17%	21%	24%	0.38
Hypertension, %	61%	60%	61%	62%	0.82
Glaucoma, %	16%	15%	16%	18%	0.74

n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness, VEGF – vascular endothelial growth factor. * Stratification by baseline VA based on inclusion criteria of major trials between (typically 19-73 letters).(Brown et al., 2010; Brown et al., 2013; Hykin et al., 2019; Korobelnik et al., 2014; Larsen et al., 2018; Scott et al., 2017) P-values: Analysis of variance (ANOVA) for continuous variables and Chi-Square or Fisher's exact test for categorical variables

Table 8.3. Baseline Demographic Characteristics by Final Treatment

	All Eyes	Monotherapy	VEGF-Switched	Steroid-Switched	P-value
Eyes, n	527	366	98	63	
Initial VEGF inhibitor:					
Bevacizumab, %	24%	20%	38%	29%	
Ranibizumab, %	43%	38%	57%	49%	
Aflibercept, %	33%	42%	5%	22%	
Female, % patients	42%	41%	45%	43%	0.76
Age, mean (SD)	71 (12)	72 (13)	70 (12)	72 (13)	0.45
VA, mean (SD)	41 (25)	41 (26)	42 (25)	38 (26)	0.51
VA < 19 letters	24%	24%	21%	30%	0.45
VA 19-73 letters *	68%	69%	66%	62%	0.53
VA > 73 letters	8%	7%	12%	8%	0.21
CST, mean (SD)	641 (233)	630 (234)	676 (242)	654 (211)	0.23
Pseudophakia, %	21%	20%	19%	33%	0.35
Hypertension, %	61%	63%	53%	63%	0.21
Glaucoma, %	16%	17%	16%	10%	0.29

n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness, VEGF – vascular endothelial growth factor. * Stratification by baseline VA based on inclusion criteria of major trials between (typically 19-73 letters).(Brown et al., 2010; Brown et al., 2013; Hykin et al., 2019; Korobelnik et al., 2014; Larsen et al., 2018; Scott et al., 2017) P-values: Analysis of variance (ANOVA) for continuous variables and Chi-Square or Fisher's exact test for categorical variables

Table 8.4. Baseline Demographic Characteristics by Completion

	All Eyes	Completers	Non-Completers	P-value
Eyes, n	527	257	270	
Initial VEGF inhibitor:				
Bevacizumab, %	24%	76 (29%)	52 (19%)	0.01*
Ranibizumab, %	43%	119 (46%)	109 (40%)	0.21
Aflibercept, %	33%	63 (24%)	109 (40%)	< 0.001*
Female, % patients	42%	43%	41%	0.66
Age, mean (SD)	71 (12)	70 (12)	73 (13)	0.03*
VA, mean (SD)	41 (25)	44 (24)	38 (26)	0.005*
VA < 19 letters	24%	19%	30%	0.003*
VA 19-73 letters *	68%	71%	65%	0.60
VA > 73 letters	8%	11%	5%	0.02*
CST, mean (SD)	641 (233)	664 (233)	617 (231)	0.02*
Pseudophakia, %	21%	15%	27%	< 0.001*
Hypertension, %	61%	60%	62%	0.81
Glaucoma, %	16%	16%	16%	0.62

n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness, VEGF – vascular endothelial growth factor. * Stratification by baseline VA based on inclusion criteria of major trials between (typically 19-73 letters).(Brown et al., 2010; Brown et al., 2013; Hykin et al., 2019; Korobelnik et al., 2014; Larsen et al., 2018; Scott et al., 2017) P-values: t-test or Wilcox test for continuous variables and Chi-Square/ Fisher's exact test for categorical variables.

8.4.2 Visual and Anatomical Outcomes

Overall, the mean VA change (95% CI) was +10 letters (7, 12) and mean CST change was -306μm (-329, -282); mean final VA was 51 letters; 44% of eyes gained and 14% lost ≥ 15 letters; 37% had VA ≥ 70 letters and 30% had VA ≤ 35 letters (Table 8.5). Two thirds of eyes received their original monotherapy only (366 [69%]). Eyes that switched between VEGF agents (98 [19%]) had similar VA gains (+11 letters) to eyes that received monotherapy (+11 letters), but with more injections (20 vs. 10 injections, respectively; $P < 0.001$) and persisted longer (76% vs. 42%, 36-month completion rate, respectively). Eyes that switched to steroid (63 [12%]), including triamcinolone in 14 eyes or dexamethasone implant in 49 eyes, had negligible change in vision over 3 years and underwent cataract surgery during the study more often (27%) than eyes not treated with steroids (11%; $P = 0.002$).

Completers (257/527 [49%]) had mean 36-month VA change (95% CI) of +12 letters (9, 15) and mean CST change of -324μm (-358, -291). The monotherapy 36-month completers (152 [29%]) had the highest mean change in VA of +14 letters (Table 8.5), but different rates of switching and non-completion made the original VEGF inhibitor groups unrepresentative by 36-months. We used longitudinal models to adjust and plot outcomes with VEGF inhibitors combined (Figure 8.1). At 2 months mean VA peaked at 56.6 letters (+15.5 letters from baseline) and mean CST reduced to 367μm (-247μm from baseline). At 36 months the mean change in VA had decreased from the peak by 4 letters (+11.4 letters from baseline) despite a further 40μm reduction in mean adjusted CST (-287μm from baseline). Our models found no differences based on VEGF inhibitor in adjusted VA beyond the first year of the study (Figure 8.2), however a distinct order of efficacy in reducing CST was found throughout the study in favour of aflibercept over ranibizumab over bevacizumab ($P < 0.001$; Figure 8.2).

Table 8.5. 36-month Outcomes in all eyes and based on treatment received.

	All Eyes	Monotherapy	VEGF-Switched	Steroid-Switched
Eyes, n, (% entire cohort)	527 (100%)	366 (69%)	98 (19%)	63 (12%)
VA Baseline, mean (SD)	41 (25)	41 (26)	42 (25)	38 (26)
VA Final, mean (SD)	51 (29)	52 (29)	54 (25)	38 (28)
VA Change, mean (95% CI)	+10 (7, 12)	+11 (8, 13)	+11 (6, 17)	0 (-7, 7)
Gain ≥ 15 letters, %	44%	45%	49%	29%
Loss ≥ 15 letters, %	14%	12%	16%	25%
VA ≥ 70 %Baseline / %Final	15% / 37%	14% / 40%	16% / 37%	16% / 19%
VA ≤ 35 %Baseline / %Final	40% / 30%	39% / 30%	43% / 22%	43% / 46%
CST Baseline, mean (SD)	641 (233)	630 (234)	676 (242)	654 (211)
CST Final, mean (SD)	335 (154)	320 (140)	343 (170)	414 (182)
CST Change, mean (95% CI)	-306 (-329, -282)	-310 (-337, -283)	-333 (-394, -273)	-240 (-315, -166)
Injections, median (Q1, Q3)	12 (6, 19)	10 (5, 17)	20 (13, 26)	12 (7, 15)
Visits, median (Q1, Q3)	20 (13, 28)	17 (10, 25)	28 (21, 32)	24 (16, 32)
Suspension at final review, n (%) *	141 (27%)	116 (32%)	15 (15%)	10 (16%)
Panretinal Photocoagulation, n (% column)	182 (34%)	106 (29%)	42 (43%)	34 (54%)
Elevated IOP requiring treatment, n (% column)	16 (3%)	10 (3%)	2 (2%)	4 (6%)
Cataract surgery performed, n (% column)	69 (13%)	41 (11%)	11 (11%)	17 (27%)
36-month Completers, n (% column)	257/527(49%)	152/366(42%)	74/98(76%)	31/63(49%)
VA Change in Completers, mean (95% CI)	+12 (9, 15)	+14 (11, 18)	+13 (7, 19)	+1 (-9, 11)
CST Change in Completers, mean (95% CI)	-324 (-358, -291)	-341 (-383, -299)	-345 (-408, -281)	-196 (-300, -92)
Injections in Completers, median (Q1, Q3)	18 (13, 24)	16 (10, 22)	22 (17, 27)	18 (15, 21)
Visits in Completers, median (Q1, Q3)	26 (22, 32)	24 (19, 29)	30 (25, 33)	30 (24, 36)

All Eyes – outcomes without censoring observations after switching and using last observation carried forward in non-completers, Monotherapy – eyes treated with initial vascular endothelial growth factor inhibitor only, VEGF-Switched – ≥ 2 alternate VEGF injections, Steroid-Switched – ≥ 1 steroid injection. n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness. Q1 – First Quartile, Q3 – Third Quartile. * No treatment observed for >180 days leading up to final review

Figure 8.1. Predicted mean VA and CST with VEGF inhibitors (combined) over 3 years with observations censored only if patients "Steroid-Switched" (A) Predicted VA and (B) Predicted CST in an average patient from our cohort with mean age (71 years) starting with mean baseline VA (41 letters) and CST (641µm). The shading represents the confidence intervals of the predicted means.

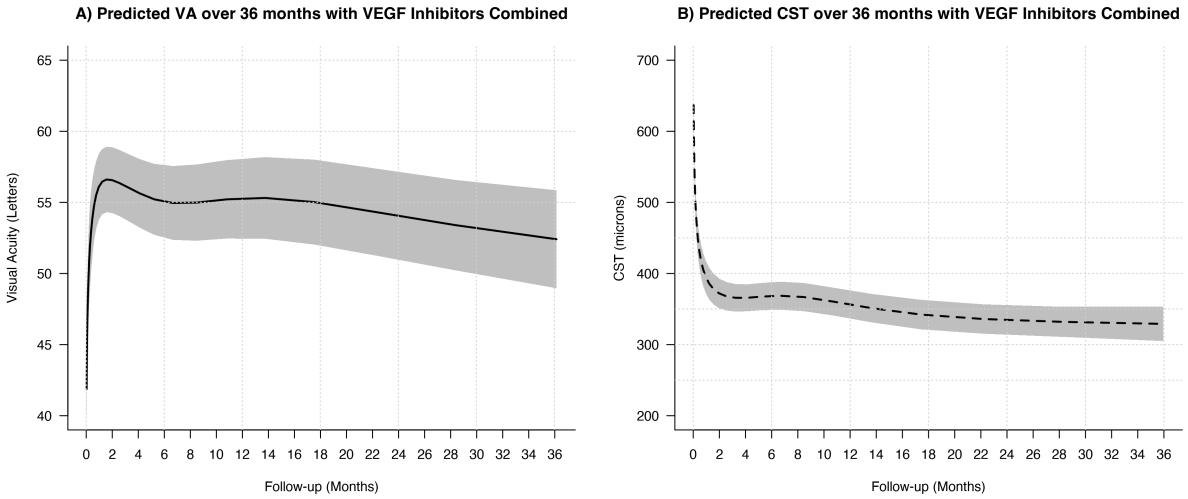

Figure 8.2. Predicted mean VA and CST by VEGF inhibitor over 3 years with observations censored after any patients "VEGF-Switched" or "Steroid-Switched". The generalized mixed effects models plot the predicted response to treatment with each VEGF inhibitor over 36 months. (A) Predicted VA and (B) Predicted CST in an average patient of mean age (71 years) starting with mean baseline VA (41 letters) and CST (641µm) treated with each VEGF inhibitor. Significant differences exist in predicted response to each VEGF inhibitor only during periods where included confidence intervals do not overlap.

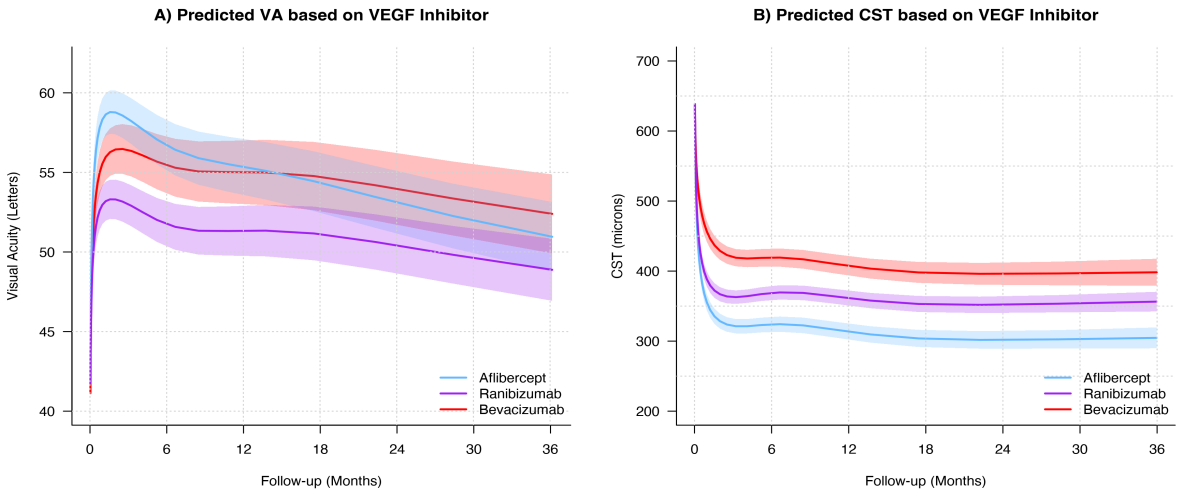

Table 8.6. 36-month Outcomes by Baseline VA grouping

	All Eyes	Very-Poor (<19 letters)	Trial-Eligible (19-73 letters)	Very-Good (>73 letters)
Eyes, n, (% entire cohort)	527 (100%)	129 (24%)	356 (68%)	42 (8%)
VA Baseline, mean (SD)	41 (25)	4 (3)	50 (14)	78 (4)
VA Final, mean (SD)	51 (29)	25 (26)	57 (24)	71 (21)
VA Change, mean (95% CI)	+10 (7, 12)	+22 (17, 26)	+7 (5, 10)	-7 (-13, -1)
Gain ≥ 15 letters, %	44%	49%	46%	7%
Loss ≥ 15 letters, %	14%	0%	18%	26%
VA ≥ 70 %Baseline / %Final	15% / 37%	0% / 8%	10% / 44%	100% / 67%
VA ≤ 35 %Baseline / %Final	40% / 30%	100% / 70%	23% / 19%	0% / 10%
CST Baseline, mean (SD)	641 (233)	749 (294)	632 (202)	447 (151)
CST Final, mean (SD)	335 (154)	300 (153)	346 (156)	326 (122)
CST Change, mean (95% CI)	-306 (-329, -282)	-448 (-505, -392)	-285 (-311, -259)	-121 (-177, -64)
Injections, median (Q1, Q3)	12 (6, 19)	7 (4, 13)	13 (7, 20)	15 (8, 22)
Visits, median (Q1, Q3)	20 (13, 28)	18 (13, 25)	21 (13, 28)	24 (14, 30)
Suspension at final review, n (%) *	141 (27%)	49 (38%)	80 (22%)	12 (29%)
Panretinal Photocoagulation, n (% column)	182 (34%)	77 (60%)	94 (26%)	11 (26%)
Elevated IOP requiring treatment, n (% column)	16 (3%)	4 (3%)	11 (3%)	1 (2%)
Cataract surgery performed, n (% column)	69 (13%)	26 (20%)	39 (11%)	4 (10%)
36-month Completers, n (% column)	257/527 (48%)	48/129 (37%)	181/356 (51%)	28/42 (67%)
VA Change in Completers, mean (95% CI)	+12 (9, 15)	+27 (19, 34)	+12 (8, 15)	-7 (-14, 0)
CST Change in Completers, mean (95% CI)	-324 (-358, -291)	-512 (-597, -427)	-314 (-350, -277)	-100 (-172, -27)
Injections in Completers, median (Q1, Q3)	18 (13, 24)	16 (8, 21)	19 (14, 24)	16 (10, 23)
Visits in Completers, median (Q1, Q3)	26 (22, 32)	25 (20, 31)	27 (22, 32)	26 (18, 33)

All Eyes – outcomes without censoring observations after switching and using last observation carried forward in non-completers, Very-Poor – eyes with baseline VA <19 letters, Trial Eligible –eyes fitting the baseline VA inclusion of the SCORE Group, Very-Good – eyes with baseline VA >73 letters, n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness. Q1 – First Quartile, Q3 – Third Quartile. * No treatment observed for >180 days leading up to final review

Outcomes grouped by baseline VA are described in Table 8.6. The two-thirds (356 [68%]) with *trial-eligible* baseline VA (19-73 letters) had mean VA change (95% CI) of +7 (5, 10) letters, mean CST change of -285μm (-311, -259), final VA in 44% was ≥ 70 letters, 19% ≤

35 letters and they received a median of 13 injections. The quarter (129 [24%]) with *very-poor* baseline VA (< 19 letters) had large mean VA and CST changes (+22 letters, -448μm), fewer injections (median, 7), lower completion rates (37%) and most (70%) had final VA ≤ 35 letters. The 44 eyes (8%) with baseline VA > 73 letters, on average, lost some vision (mean, -7 letters), had smaller changes in CST (-121μm), more injections (median, 15), higher completion rates (67%) and the majority (67%) had final VA ≥ 70 letters.

8.4.3 Treatments and Visits

The 36-months completers (257 eyes [49%]) had a median of 18 (13, 24) injections and 26 visits in 3 years (Table 8.5). Eyes that completed 1, 2 and 3 years had a mean of 7.6, 4.9 and 4.2 injections in each of those years, respectively. The entire cohort received a median (Q1, Q3) of 12 (6, 19) injections, with 20 (13, 28) visits during the study. One-third of eyes (182/527 [34%]) were treated with pan-retinal photocoagulation (PRP), these eyes had lower mean baseline VA (32 letters), lower mean final VA (35 letters) but no significant difference in frequency of injections ($P = 0.74$) compared with the eyes that did not receive PRP. We found no difference in outcomes including injections and visits in eyes commencing treatment in 2018 that were in part managed during the COVID-19 pandemic (2020) (Zarranz-Ventura et al., 2022).

Suspension of therapy lasting over 180 days occurred in 223/527 eyes (42%) during the 3-year study. In 141 eyes (27%, 62 completers, 79 non-completers) the suspension continued to final review, VA and CST changed little after ceasing treatment (mean, +2 letters, -41μm), mean final VA change was +11 letters from baseline, but the final VA had a bimodal distribution (40% ≥ 70 letters, 41% ≤ 35 letters). Only sixty-five (12%) eyes suspended with CST consistently remaining below 300μm, also with a bimodal distribution of final VA (48% ≥ 70 letters, 37% ≤ 35 letters).

In 82 eyes (15%) the suspension was only temporary, during which there was a deterioration in mean VA of -9 letters (from 58 letters to 49 letters) and CST of +51μm (from 360μm to 411μm) – despite restarting treatment – mean final VA change was only +2 letters from baseline in these eyes.

Predicting outcomes of non-completers required inference while acknowledging that some patients likely continued to receive therapy outside the registry. We used suspensions (27%) as the marker for cessation, but many non-completers were not followed for 6 months after their last recorded injection to qualify (mean follow-up after last injection, 149 days). Treatment between 30-36 months was documented in 195 completers (37%), however when we accessed all available follow-up, 33 of these eyes (6%) had no further treatment after their last injection during the final 6 months of the study. When combined with reasons given for discontinuation (below) that indicated cessation, we established treatment status (ongoing or ceased) in 319/527 (61%) of participants – 165 patients (31%) were still requiring treatment at 3 years and 154 patients (29%) had concluded treatment before 3 years.

8.4.4 Switching

Switching occurred in 160 eyes (30%). Switching rates differed significantly from the initial VEGF inhibitor (bevacizumab 43%, ranibizumab 38%, aflibercept 11%; $P < 0.001$, Figure 8.3). Half of all switching was to aflibercept (79 eyes, 15%). Two strong patterns of VEGF switching reflected increasing availability of drugs during the study: from bevacizumab (29/128, 23%) to ranibizumab and from ranibizumab (68/227, 30%) to aflibercept. Specific switching outcomes are described in Table 8.7.

Table 8.7. Switching outcomes at time of switch and final review

Original VEGF group	Switched between VEGF agents			Switched to a Steroid agent	
	To: Bevacizumab	To: Ranibizumab	To: Aflibercept	To: Triamcinolone	To: Dexamethasone
Bevacizumab initially					
Eyes (% of original group) *		26 (20%)	18 (14%)	11 (9%)	7 (5%)
VA Switch, mean (SD)		44 (24)	58 (18)	45 (16)	51 (20)
VA Final, mean (SD)		47 (26)	67 (16)	57 (18)	35 (29)
VA Change after Switch, mean (SD)		3 (14)	9 (17)	13 (12)	-16 (20)
CST Switch, mean (SD)		474 (170)	509 (194)	653 (214)	688 (198)
CST Final, mean (SD)		348 (163)	353 (185)	385 (120)	561 (223)
CST Change after Switch, mean (SD)		-126 (202)	-153 (232)	-268 (183)	-127 (231)
Ranibizumab initially					
Eyes (% of original group) *	7 (3%)		61 (27%)	2 (1%)	29 (13%)
VA Switch, mean (SD)	34 (27)		51 (23)	44 (13)	34 (24)
VA Final, mean (SD)	30 (35)		52 (25)	40 (53)	29 (28)
VA Change after Switch, mean (SD)	-4 (16)		1 (18)	-4 (40)	-4 (22)
CST Switch, mean (SD)	509 (303)		462 (198)	702 (49)	489 (202)
CST Final, mean (SD)	435 (191)		342 (157)	482 (238)	386 (175)
CST Change after Switch, mean (SD)	-74 (257)		-119 (256)	-220 (288)	-103 (244)
Aflibercept initially					
Eyes (% of original group) *	0 (0%)	8 (5%)		1	13 (8%)
VA Switch, mean (SD)		38 (25)		60	42 (24)
VA Final, mean (SD)		32 (25)		71	38 (28)
VA Change after Switch, mean (SD)		-6 (14)		11	-3 (19)
CST Switch, mean (SD)		450 (213)		708	487 (190)
CST Final, mean (SD)		420 (244)		267	396 (180)
CST Change after Switch, mean (SD)		-31 (372)		-441	-91 (228)

VA = visual acuity in log MAR letters, CST = central subfield thickness in microns. * Note that percentages do not necessarily add to 100% because some eyes switched more than once (between VEGF agents and/or to Steroid).

8.4.5 Non-completion of 36 Months

Non-completers (270/527, 51%; Table 8.8) had mean VA change (95% CI) of +7 (4, 10) letters, mean (SD) final VA 45 letters (30), 39% gained ≥ 15 letters, 17% lost ≥ 15 letters; 32% had VA ≥ 70 letters, 38% had VA ≤ 35 letters and mean change in CST was -288μm after a median (Q1, Q3) of 7 (4, 12) injections over 18 (12, 26) months. Non-completion rates were higher with aflibercept ($P = 0.001$, Figure 8.3), but aflibercept non-completers had a higher mean VA change (+10 letters) than ranibizumab (+6 letters) or bevacizumab (+7 letters) non-completers ($P = 0.003$). Non-completion was associated with higher baseline

age ($P = 0.03$), lower baseline VA ($P = 0.005$) and lower baseline CST ($P = 0.02$, Table 8.S4). Discontinuation reasons were available in 102 eyes (38% of 270 non-completers) – 39 transferred care to another physician, 5 had “treatment successful”, 14 “declined treatment”, 2 had “medical contraindications” and in 8 “further treatment was futile” and 34 patients died on active treatment.

Figure 8.3. Kaplan-Meier survival curves describing time to A) switching from the original VEGF inhibitor and B) Non-completion of 36 months by initial VEGF inhibitor.

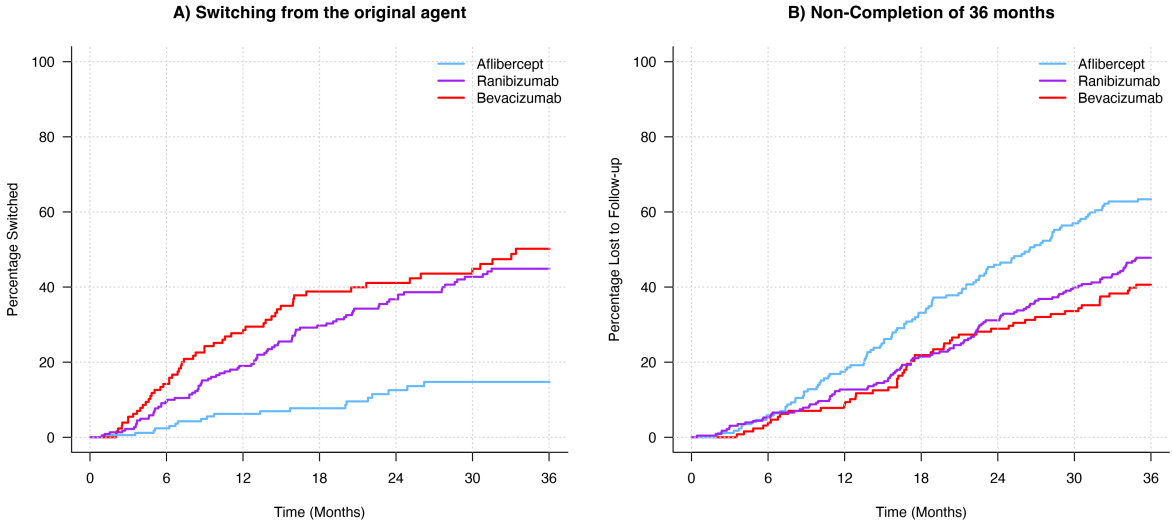

Table 8.8. Outcomes in Non-Completers by Treatment received.

	All Non-Completers	Monotherapy Non-Completers	VEGF-Switched Non-Completers	Steroid-Switched Non-Completers
Eyes, n, (% entire cohort)	270 (51%)	214 (41%)	24 (4%)	32 (6%)
VA Baseline, mean (SD)	38 (26)	39 (26)	38 (27)	30 (28)
VA Final, mean (SD)	45 (30)	47 (30)	45 (31)	29 (26)
VA Change, mean (95% CI)	+7 (4, 10)	+8 (5, 11)	+8 (-9, 24)	-1 (-11, 9)
Gain ≥ 15 letters, %	39%	40%	46%	25%
Loss ≥ 15 letters, %	17%	14%	29%	25%
VA ≥ 70 %Baseline / %Final	13% / 32%	12% / 35%	17% / 33%	12% / 12%
VA ≤ 35 %Baseline / %Final	44% / 38%	42% / 36%	50% / 33%	53% / 59%
CST Baseline, mean (SD)	617 (231)	601 (224)	668 (268)	682 (235)
CST Final, mean (SD)	329 (156)	315 (142)	368 (212)	395 (181)
CST Change, mean (95% CI)	-288 (-320, -255)	-286 (-321, -252)	-300 (-452, -149)	-286 (-392, -180)
Injections, median (Q1, Q3)	7 (4, 12)	6 (4, 12)	13 (9, 15)	8 (5, 12)
Visits, median (Q1, Q3)	14 (9, 20)	12 (8, 18)	18 (17, 24)	18 (14, 23)
Final month of follow-up, median (Q1, Q3)	18 (12, 26)	17 (10, 25)	22 (16, 29)	23 (17, 30)
Suspension at final review, n (% column) *	79 (29%)	69 (32%)	4 (17%)	6 (19%)
Panretinal Photocoagulation, n (% column)	91 (34%)	63 (29%)	11 (46%)	17 (53%)
Elevated IOP requiring treatment, n (% column)	9 (3%)	7 (3%)	1 (4%)	1 (3%)
Cataract surgery performed, n (% column)	22 (8%)	16 (7%)	3 (12%)	3 (9%)

All non-completers – outcomes without censoring observations after switching and using last observation carried forward, Monotherapy – eyes treated with initial vascular endothelial growth factor inhibitor only, VEGF-Switched – ≥ 2 alternate VEGF injections, Steroid-Switched – ≥ 1 steroid injection. n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness. Q1 – First Quartile, Q3 – Third Quartile, IOP – Intraocular pressure. * No treatment observed for >180 days leading up to final review and loss to follow-up

8.4.6 Adverse outcomes

New macular changes were recorded in 67 (13%) eyes (epiretinal membrane, macular hole, pigment clumping or atrophy). Neovascular complications occurred in 68 (13%) eyes including rubeotic glaucoma in 22 (4%) eyes. Eyes with *very-poor* baseline VA (< 19 letters) more often had neovascular complications (31%; $P < 0.001$) or macular changes (25%; $P <$

0.001). There was one retinal detachment (final VA 85 letters), one case of infectious endophthalmitis (count fingers) and two cases of non-infectious endophthalmitis (51 and 79 letters) following a total of 7022 injections in the study.

8.5 Discussion

We analysed data from the FRB! observational database to describe 3-year outcomes in 257 eyes for which data were available out of a total of 527 treatment-naïve CRVO eyes commenced on aflibercept, ranibizumab or bevacizumab in routine clinical practice. In this portion of eyes with follow-up out of a broad cohort derived from routine care, the overall mean change in VA at 36-months was +12 letters and macular thickness improved by a mean of -324μm from baseline, but the outcomes for the overall group of 527 eyes is likely to be worse because eyes with poor outcome may be more likely to be lost to follow up. On average, patients in our study received 12 injections, one third achieved good VA (≥ 70 letters) and one third poor VA (≤ 35 letters). Ongoing treatment was documented at 3 years in 31% of our cohort however we were able to infer cessation of therapy in 29% before 3 years.

This study improves prognostication out to 3 years for patients starting available VEGF therapy for CRVO in routine care. Current RWE suffers from very high rates of dropout or analyses completers only (Chatziralli et al., 2018; Spooner et al., 2019; Wu et al., 2022). Follow-up in this study was 49% at 3 years, which was far higher than comparable studies (Gale et al., 2020). We believe it is important to account for the outcomes of all eyes whether they were completers (49%, +12 letters, -324µm, 18 injections) or non-completers (51%, +7 letters, -288μm, 7 injections) as there is potential for selection bias in “completers-only analyses” especially as outcomes may further deteriorate in eyes that drop out. The 18 injections at 26 visits over 3 years that we found for completers is a high treatment burden. Better outcomes may be achieved with longer lasting agents. On-going efforts to treat the

causal pathology as well as the sequelae of the venous obstruction in CRVO should continue (McAllister, Smithies, Chen, Mackey, & Sanfilippo, 2018, 2021).

Starting VA is one of the strongest predictors of outcomes first reported by the CVOS group, considering ischaemic and non-ischaemic subtypes together ("Natural history and clinical management of central retinal vein occlusion. The Central Vein Occlusion Study Group," 1997). One-quarter of our cohort had *very-poor* baseline VA < 19 letters, in keeping with CVOS, 70% had final VA ≤ 35 letters, but with so much room for improvement (mean, +22 letters) these eyes lifted the overall primary outcome of mean change in VA in our study. Most trials require baseline VA between 19-73 letters for inclusion (Brown et al., 2010; Brown et al., 2013; Hykin et al., 2019; Korobelnik et al., 2014; Larsen et al., 2018; Scott et al., 2017). A subset of eyes in our study with *trial-eligible* baseline VA (19-73 letters [68%]) had mean change in VA of +7 letters, less than our overall cohort and the RCT extension studies which had improvements of around +14 letters at 3-4 years (Campochiaro et al., 2014; Iftikhar et al., 2019). Unfortunately, outside the strict controls of RCTs the results achieved in everyday practice are generally less as seen with this study.

An estimation of the number of patients with CRVO who could discontinue treatment within 3 years was a major outcome of this study. We had to infer cessation from suspensions of therapy and reasons specifically given for discontinuation available in 102/270 (38%) non-completers that were indicative of cessation. The final treatment status (ongoing or ceased) was identified in 61% of our cohort. Our estimate that an equal number of eyes were still requiring treatment after 3 years is similar to that of the RETAIN extension study (Campochiaro et al., 2014). Unlike the RETAIN study, we found very few eyes (68/527 [12%]) achieved oedema resolution while off treatment. We observed an erosion of VA gains from a peak at 2 months to 36 months. This trend may well continue if persistent oedema is inadequately treated in subsequent years (Iftikhar et al., 2019).

We observed a more lenient approach to treatment of CME in this real-world study. Tolerance of CME is not in keeping with either a *pro-re-nata* or a *treat-and-extend* regime, both of which advocate treatment in the presence of active disease. Tolerance of CME was most apparent during suspensions of therapy in what appeared to be attempted withdrawal of treatment in many eyes. These periods of 6 or more months without treatment either continued to final review with maintenance of VA and CST or they ended with treatment being restarted because VA and CST deteriorated unacceptably without treatment. The bimodal distribution of VA in eyes that suspended therapy hinted at either successful conclusion or futility of further treatment.

We have previously reported superiority of aflibercept over ranibizumab at 12 months in CRVO using models predicting VA and CST response (Niedzwiecki et al., 2021). In this study, a similar approach was used over 36-months that included bevacizumab. We found no significant drug-based difference in predicted VA beyond the first year, similar to other 2-year comparative analyses, extending support for all three agents as viable treatments over 3 years (Hykin et al., 2019; Scott et al., 2019). We did however find that aflibercept was better at reducing macular thickness than ranibizumab throughout 36 months, while bevacizumab was least effective.

This study has some limitations inherent in its observational design. Even though no significant demographic differences existed in drug groups at baseline we focused on a descriptive analysis that effectively pooled eyes treated with VEGF inhibitors including few select eyes that received steroids for completeness. We wanted to identify in a large real-world cohort recruited at baseline the ongoing need for therapy at 3 years. A simple goal but a task made difficult due to dropout. We have data on a significant number of dropouts, albeit still a minority but enough to make valid estimates of what the reasons were in the entire dropout cohort so that our general estimates of the requirement for ongoing treatment are likely accurate. We used models to impute outcomes in non-completers and switchers to

avoid overusing last observation carried forward. The models compared agents utilising the entire cohort rather than the unadjusted outcomes of monotherapy completers which were eroded differently by switching and non-completion. Why one agent was started over another is unknown but was likely based on availability, as was switching. This study complements but does not try to emulate the experimental design of RCTs – it offers a 3-year overview of outcomes in eyes that start VEGF therapy with CRVO in routine clinical care. The RVO module of the FRB! registry records only a minimum essential outcome set. It has high data finalization (95%) rates, and FRB! physicians agree to enter data on at least 85% of relevant patients when they participate making the results of our study generalizable to a broad population.

This study illustrates the large investment in time and treatment required to achieve reasonable visual outcomes in patients with CRVO encountered in routine clinical practice. Treatment was more intensive in the first year then tapered off in the second and third years (mean of 8, 5 and 4 injections, respectively). We did not find any difference in VA outcomes among the 3 available drugs, however eyes treated with aflibercept had larger reductions in CST. It appears that around half of patients starting injections for CRVO will still be needing them 3 years later to maintain their vision. There was a significant non-completer rate of 51% with cessation of treatment linked to resolution of the occlusion seen only in a small percentage. Tolerating some disease activity without treatment may be acceptable in some patients, in others the burden of therapy and what may be perceived as a less than satisfactory visual response causes a significant number to give up or fail to attend.

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CHAPTER 9: THREE-YEAR OUTCOMES OF VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS IN NAÏVE BRANCH RETINAL VEIN OCCLUSION: FIGHT RETINAL BLINDNESS!

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9.1 Abstract

Purpose: To evaluate the 3-year outcomes of vascular endothelial growth factor (VEGF) inhibitors in the treatment of cystoid macular oedema (CME) due to branch retinal vein occlusion (BRVO) in an international multicentre cohort of eyes.

Design: Multicentre, international, BRVO database study.

Methods: Demographics, visual acuity (VA) in logarithm of the minimum angle of resolution (log MAR) letters, central subfield thickness (CST), treatments, number of injections and visits data was collected using a validated web-based tool.

Main outcomes measures: Visual acuity (VA) gain at 3 years in LogMAR letters. Secondary outcome measures included anatomical results, treatment pattern and percentage of completers. A subgroup analysis by study drug was conducted for clinical outcomes.

Results: Mean adjusted VA change was +11 letters (95% CI 9,13), mean adjusted change in CST was -176μm (-193, -159). Median number of injections/visits was 16/24 at 3 years of follow-up. Most eyes received VEGF inhibitors exclusively (89%, n=677) and as a monotherapy in 71% (n=538). Few eyes were switched to steroids (11%, n=83). Suspensions in treatment > 180 days occurred in 26% of study eyes. Aflibercept showed greater CST reductions (-147 vs -128 vs -114μm; $P < 0.001$) and significantly lower switching rates (14% vs 38% vs 33%, $P < 0.001$) compared with ranibizumab and bevacizumab, respectively.

Conclusions: This international study of 3-year BRVO outcomes after starting treatment with VEGF inhibitors found adequate visual and anatomical results in routine clinical care.

Visual outcomes were similar amongst the different initiating VEGF inhibitors, although eyes starting with aflibercept had better anatomical outcomes and a lower switching rate.

9.2 Introduction

Intravitreal vascular endothelial growth factor (VEGF) inhibitors are the current first-line treatment option for the management of cystoid macular oedema (CME) secondary to branch retinal vein occlusion (BRVO) (Flaxel et al., 2020; Schmidt-Erfurth et al., 2019). The efficacy of aflibercept and ranibizumab was demonstrated in randomized controlled trials (RCT) with strict inclusion and exclusion criteria - which do not always reflect the broader population treated in routine clinical care (Brown et al., 2011; Campochiaro et al., 2010; Clark et al., 2016). There is increasing interest in real-world data studies (RWD) to address this knowledge gap as their findings are representative of the wide cohort of patients who are treated with these agents (Ang et al., 2020; Chatziralli et al., 2018; Dalan et al., 2020; Nanji et al., 2022; Shalchi, Mahroo, Bunce, & Mitry, 2020). To date, most RWD on VEGF inhibitors for BRVO are retrospective cohorts of patients from single centres (Salinas-Alamán et al., 2011; Winterhalter et al., 2018). Invariably, the outcomes achieved in these RWD are inferior to those observed in RCTs, often due to a reduced number of injections being delivered (Ang et al., 2020; Nanji et al., 2022).

One significant limitation of existing RWD is the short duration of the follow-up and this is particularly relevant to the outcome of treatment with VEGF inhibitors which are short acting therapies requiring frequent reinjections to maintain treatment efficacy. To compound the short duration of follow-up, the completion rate in many existing RWD is low with drop-out rates of up to 50-80% being reported. In the Luminous study (n= 326 eyes) 54% were lost to follow-up at 12 months, and in the United Kingdom Electronic Medical Records (EMR) users group national report (n= 5661), the lost to follow-up rate was 80% (Gale et al., 2021; Pearce et al., 2020). These factors significantly limit the evaluation of outcomes achieved by these agents in routine clinical care, particularly when evaluating their efficacy beyond 12 months.

The Fight Retinal Blindness (FRB!) registry is an international multicentre project which consists of an audit tool for the collection of clinical data from patients receiving treatment with intravitreal therapies (Gillies et al., 2014). This platform has allowed the collection of large datasets of eyes treated with VEGF inhibitors for neovascular age-related macular degeneration, diabetic macular oedema or retinal vein occlusion (Bhandari et al., 2020; Zarranz-Ventura, Nguyen, et al., 2022; Zarranz-Ventura, Parrado-Carrillo, et al., 2022). We have recently reported the 12-month clinical outcomes achieved with VEGF inhibitor drugs, bevacizumab (Wang et al., 2022), ranibizumab and aflibercept (Hunt et al., 2022).

We investigated the real-world long-term outcomes achieved with VEGF inhibitors in an international multicentre cohort of treatment-naïve BRVO eyes treated and followed for up to 3 years. The treatment patterns, switching strategies, dropout rates, and possible inter-drug differences in the visual and anatomical outcomes in routine clinical care were assessed.

9.3 Materials And Methods

9.3.1 Study Design and Setting

This was a database observational study using the Fight Retinal Blindness! (FRB!) registry (Gillies et al., 2014). We analysed the anonymized data captured from routine practice retrospectively adhering to the tenets of the Declaration of Helsinki, following the STROBE checklists for reporting observational studies and without interfering with treatment decisions made by physicians in consultation with their patients (von Elm et al., 2008). The web-based RVO module of the FRB! registry collects a prospectively defined, minimum, patient-centred outcomes set with mandatory fields populated at each clinical visit that are numeric, mutually exclusive or from a drop-down menu. Enrolment required a baseline visit (defined as the first treatment visit) that recorded the type of RVO, presence or absence of key risk factors in addition to parameters common to all subsequent visits including the logarithm of the

minimum angle of resolution (log MAR) visual acuity (best of uncorrected, corrected or pinhole) expressed in letters, central subfield thickness (CST [μm]), assessed with optical coherence tomography using the same machine for the same patient throughout, treatments given, procedures performed and adverse events.

9.3.2 Patient Selection and Definitions

We included in the analysis all treatment-naïve patients with BRVO that commenced treatment with either bevacizumab (1.25 mg Avastin; Genentech, Inc., CA, USA/Roche, Basel, Switzerland), aflibercept (2mg Eylea, Bayer) or ranibizumab (0.5mg Lucentis, Genentech Inc/Novartis) between 1st June 2010 and 1st June 2020. Central and Hemi-retinal vein occlusions were excluded. Eligible patients must have had at least three injections. Treatment regimens were driven by local guidelines according to routine clinical care. “Completers” were defined by follow-up ≥ 1095 days. Treatment during the 3-year study was either “Monotherapy” (the original VEGF only), “VEGF-Switched” (≥ 2 alternate VEGF injections) or “Steroid-Switched” (≥ 1 steroid injection). “Suspension” of therapy was arbitrarily defined as observed periods without an injection for over 180 days.

Ethics and data protection approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09, Australia and New Zealand); the Caldicott Guardian (Sept 2024, United Kingdom); Mater Private Hospital, Dublin (IRB, 1/378/2130, Ireland); Comité Etico de Investigación Medica, Barcelona (HCB/2018/0123, Spain); IRCCS Cà Granda Foundation Maggiore Policlinico Hospital (Italy); Société Française d’Ophtalmologie (2017_CLER-IRB_II-05, France). Local ethics committees approved consent as “opt-in” in European centers and “opt-out” in Australia and New Zealand. Due to the non-interventional nature of the registry, approval of the registry in the Netherlands was not needed according to the Medical Ethics Committee of the Academic Medical University Centre, the Netherlands.

9.3.3 Outcomes

The primary outcome measure was mean change in VA 36 months after the first treatment visit. Secondary outcomes included percentage of eyes with final VA ≥ 70, VA ≤ 35 letters, VA gain or loss ≥ 15 letters; mean change in CST; suspensions of therapy; visits and injections; non-completion; switching and adverse events.

9.3.4 Statistical analysis

Data were summarised with descriptive statistics, including counts and percentages for categorical variables; and mean, standard deviation (SD), 95% confidence intervals (CI), median with first and third quartiles (Q1, Q3) for continuous variables. Observations began at the first treatment visit and continued until the 36-month visit (1095 +/- 90 days). We compared VEGF agents using longitudinal models to predict VA and CST outcomes had all eyes maintained their original therapy through 36 months. The models were built using all available observations while eyes were in receipt of their original drug. Adjustments for baseline age, baseline VA (or CST) were fixed effects. Practice location and bilaterality were considered random effects. This was preferred over comparing select eyes still receiving their original drug at 36-months because switching and non-completion eroded the original drug groups differently.

Unadjusted outcomes were reported in all eyes and based on treatment received (Monotherapy, VEGF-Switched or Steroid-Switched), observations were not censored after switching and last observation was carried forward in non-completers. Outcomes in switchers at the time of switch and at final review were also reported. Kaplan-Meier survival curves were generated for switching and non-completion with Cox-proportional hazards models comparing VEGF agents.

R version 4.2.3 (http://www.R-project.org/) was used for statistical analysis utilising the *mgcv* (V1.9-0) and *itsadug* (V2.4.1) packages for generalized additive mixed effects models, the *survival* (3.5-7) package to generate event based outcomes and *coxme* (2.2-18.1) for comparing Kaplan-Meier estimates by drug (R Core Team, 2020).

9.4 Results

9.4.1 Study Participants

We identified 760 treatment naïve eyes with CMO due to BRVO that started VEGF inhibitors between 1st June 2010 and 1st June 2020 (Table 9.1). Baseline mean (SD) age was 71 years (11), mean VA was 57 letters (18) and mean CST was 479μm (162) overall. Demographics were broadly similar between groups whether stratified by initial VEGF inhibitor or by the treatment they received over 3 years (Tables 9.2 and 9.3).

Table 9.1. Baseline Demographics of Patients with BRVO included in the Study.

Eyes, n	760
Patients, n	747
Initial VEGF inhibitor: Bevacizumab, n (%) Ranibizumab, n (%) Aflibercept, n (%)	 252 (33%) 273 (36%) 235 (31%)
Female, % patients	53%
Age, mean (SD)	71 (11)
Baseline VA, mean (SD) letters ≥ 70 letters, %* ≤ 35 letters, %	57 (18) 30% 13%
Baseline CST, mean (SD), μm	479 (162)
Hypertension, %	66%
Glaucoma, %	7%
Pseudophakia, %	19%
n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness, VEGF – vascular endothelial growth factor inhibitors including.	

Table 9.2. Baseline Demographic Characteristics by Initial VEGF inhibitor.

	All Eyes	*Bevacizumab*	*Ranibizumab*	*Aflibercept*	*P-value*
Eyes, n	760	252	273	235	
Patients, n *(%)*	747	249	272	231	
Female, % patients	53%	52%	49%	59%	0.09
Age, mean (SD)	71 (11)	71 (11)	70 (12)	71 (11)	0.67
Baseline VA, mean (SD) letters	57 (18)	58 (17)	57 (18)	58 (18)	0.69
*≥ 70 letters, %**	30%	27%	31%	33%	0.30
≤ 35 letters, %	13%	11%	15%	14%	0.35
Baseline CST, mean (SD), *μ*m	479 (162)	494 (166)	478 (165)	464 (152)	0.14
Hypertension, %	66%	71%	66%	60%	0.06
Glaucoma, %	7%	7%	7%	7%	0.95
Pseudophakia, %	19%	20%	18%	19%	0.91

n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness, VEGF – vascular endothelial growth factor inhibitors including.

Table 9.3. Baseline Demographic Characteristics by Treatment Received.

	All Eyes	*Monotherapy*	*VEGF-Switched*	*Steroid-Switched*	*P-value*
Eyes, n	760	538	139	83	
Patients, n *(%)*	747	532	137	83	
Female, % patients	53%	55%	47%	49%	0.14
Age, mean (SD)	71 (11)	71 (12)	69 (11)	69 (9)	0.14
Baseline VA, mean (SD) letters	57 (18)	57 (18)	57 (19)	59 (15)	0.59
≥ 70 letters, %	30%	30%	32%	28%	0.69
≤ 35 letters, %	13%	14%	14%	8%	0.44
Baseline CST, mean (SD), *μ*m	479 (162)	479 (162)	473 (151)	494 (179)	0.69
Hypertension, %	66%	66%	66%	64%	0.98
Glaucoma, %	7%	7%	9%	2%	0.21
Pseudophakia, %	19%	18%	24%	16%	0.19

n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness, VEGF – vascular endothelial growth factor inhibitors including.

9.4.2 Visual and Anatomical Outcomes

In all eyes, 36-month crude mean change (95%CI) in VA was +11 letters (10, 12) and CST was -169*μ*m (-182, -156). Mean final VA (SD) was 68 (18) letters, 41% of eyes gained and 7% lost ≥ 15 letters; 63% had VA ≥ 70 letters; 7% had VA ≤ 35 letters (Table 9.4). Response to VEGF inhibitors combined was plotted in Figure 9.1 (censoring only after steroids). We

used models to compare response to each VEGF inhibitor (censoring after any switch) and found no difference in adjusted change in VA despite a significantly greater adjusted mean change in CST with aflibercept monotherapy (-147μm), over ranibizumab monotherapy (-128μm) and bevacizumab monotherapy (-114μm; $P < 0.01$; Figure 9.2).

Table 9.4. Three-year Outcomes in all eyes and based on treatment received.

	All Eyes	Monotherapy	VEGF-Switched	Steroid-Switched
Eyes, n, (% entire cohort)	760 (100%)	538 (71%)	139 (18%)	83 (11%)
VA Baseline, mean (SD)	57 (18)	57 (18)	57 (19)	59 (15)
VA Final, mean (SD)	68 (18)	70 (17)	68 (18)	55 (24)
VA Change, mean (95% CI)	11 (10, 12)	13 (12, 15)	11 (8, 15)	-4 (-10, 2)
Gain ≥ 15 letters, %	41%	44%	41%	19%
Loss ≥ 15 letters, %	7%	4%	6%	28%
VA ≥ 70 %Baseline / %Final	30% / 63%	30% / 67%	32% / 60%	28% / 39%
VA ≤ 35 %Baseline / %Final	13% / 7%	14% / 5%	14% / 6%	8% / 18%
CST Baseline, mean (SD)	479 (162)	479 (162)	473 (151)	494 (179)
CST Final, mean (SD)	311 (110)	295 (90)	331 (113)	384 (175)
CST Change, mean (95% CI)	-169 (-182, -156)	-184 (-199, -169)	-142 (-173, -111)	-110 (-157, -62)
Injections, median (Q1, Q3)	11 (6, 19)	10 (6, 17)	18 (11, 25)	11 (7, 15)
Visits, median (Q1, Q3)	19 (12, 26)	16 (10, 23)	25 (18, 32)	25 (20, 30)
Suspension at final review, n (% column) *	198 (26%)	149 (28%)	28 (20%)	21 (25%)
Focal laser treatment, n (% column)	78 (10%)	49 (9%)	18 (13%)	11 (13%)
Sectoral Photocoagulation, n (% column)	136 (18%)	76 (14%)	34 (24%)	26 (31%)
Elevated IOP requiring treatment, n (% column)	25 (3%)	8 (1%)	6 (4%)	11 (13%)
Cataract surgery performed, n (% column)	84 (11%)	43 (8%)	9 (6%)	32 (39%)
36-month Completers, n (% column)	416 (55%)	256 (48%)	100 (72%)	60 (72%)
VA Change in Completers, mean (95% CI)	11 (9, 13)	13 (11, 16)	14 (9, 18)	-3 (-9, 4)
CST Change in Completers, mean (95% CI)	-176 (-193, -159)	-192 (-213, -170)	-156 (-190, -122)	-138 (-184, -93)
Injections in Completers, median (Q1, Q3)	16 (9, 22)	15 (9, 21)	22 (14, 28)	10 (7, 15)
Visits in Completers, median (Q1, Q3)	24 (19, 30)	23 (17, 29)	27 (22, 34)	26 (22, 32)

All Eyes – outcomes without censoring observations after switching and using last observation carried forward in non-completers, Monotherapy – eyes treated with initial vascular endothelial growth factor inhibitor only, VEGF-Switched – ≥ 2 alternate VEGF injections, Steroid-Switched – ≥ 1 steroid injection (10 eyes - triamcinolone, 73 eyes - dexamethasone implant). n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness. Q1 – First Quartile, Q3 – Third Quartile, IOP – Intraocular pressure. * No treatment observed for >180 days leading up to and including 36-months or final review in non-completers

Figure 9.1. Mean VA and CST with VEGF inhibitors combined. Observations from all eyes while receiving VEGF inhibitors only (original or alternate, observations after receipt of any steroid were censored). The plot is smoothed with the mean surrounded by 95% confidence intervals (1.96*SE).

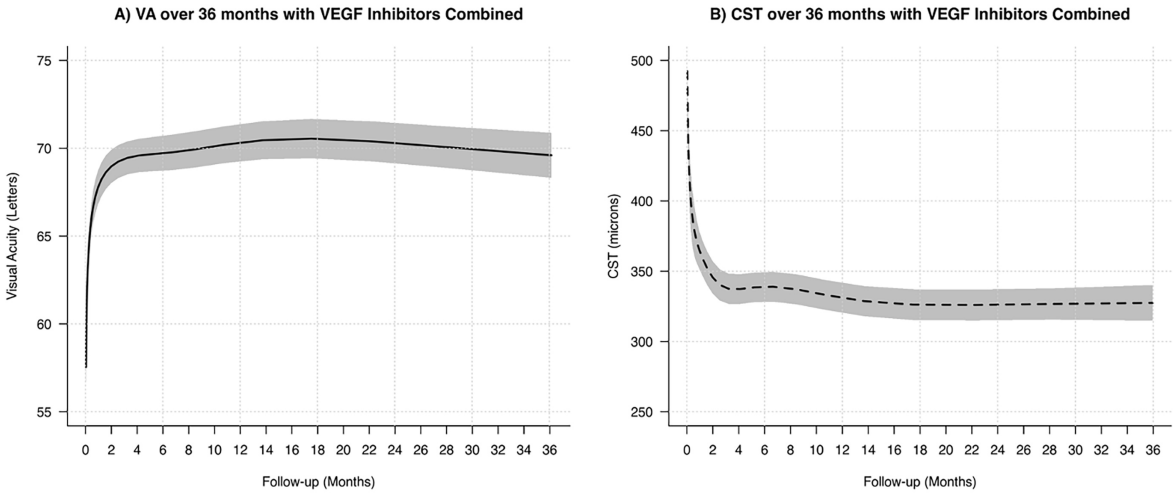
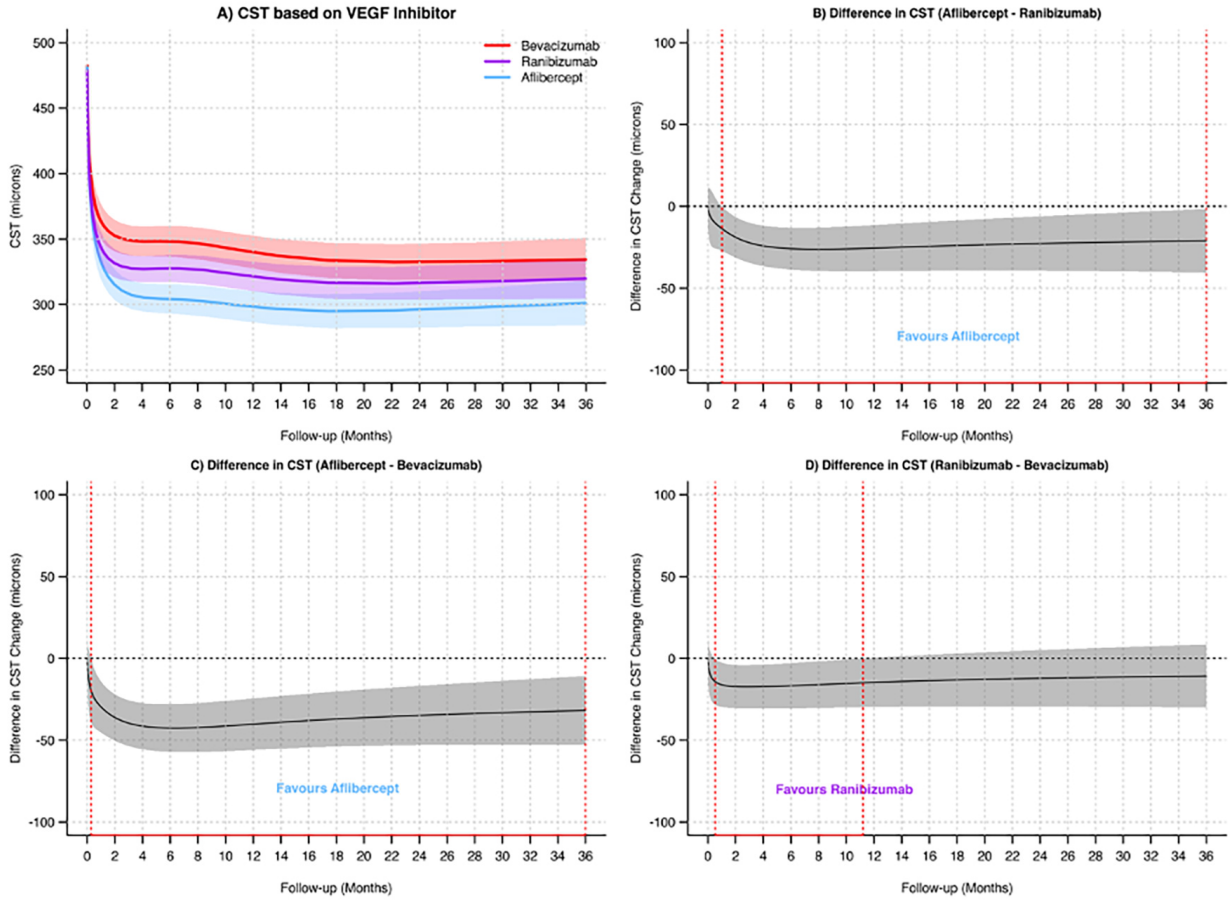


Figure 9.2. Mean CST by VEGF inhibitor over 3 years. Significant drug-based differences in predicted CST in Figure 9.2A occurred throughout 36 months. Subtracting predictions, with 95% confidence intervals (1.96*SE) included in Figure 9.2B-D, are in favor of aflibercept over ranibizumab over bevacizumab (dashed red lines indicate periods of significant difference when confidence intervals are not overlapping).



9.4.3 Treatments, Visits and Suspensions of Therapy

The majority of eyes only had VEGF inhibitors (677 [89%]), mostly their original agent (538 [71%]) or an alternate VEGF inhibitor (139 [18%]). Few eyes switched to steroids (83 [11%]; 10 triamcinolone, 73 dexamethasone implant). The entire cohort received a median (Q1, Q3) of 11 (6, 19) injections, at 19 (12, 26) visits during the 36-month study. The completers (416/760 [55%]) had a median of 16 (9, 22) injections at 24 visits (Table 9.4). The mean number of injections of any agent given in the 1st, 2nd and 3rd year was 7.7, 4.7 and 4.1 in eyes that completed each of those years respectively. Other treatments included sectoral photocoagulation delivered in 136/760 (18%) eyes, unrelated to the total number of VEGF injections given in 3 years (median, 13 injections), but more often in eyes switched to steroids than eyes not switched to steroids (29% vs. 18%; $P = 0.01$); and focal laser delivered in 78/760 (10%) eyes that achieved a mean final VA of 71 letters, but these eyes required more injections than the wider cohort (23 vs. 12 injections; $P < 0.01$). Posterior segment neovascularisation occurred in 18 patients that received fewer injections than average (8 vs. 11 injections; $P = 0.04$), were treated with sectoral photocoagulation and had mean final VA of 73 letters.

Suspensions of therapy lasting over 180 days during the 3-year study occurred at least once in 331/760 (44%) eyes. In 198 eyes (26%), the suspension continued to final review, a mean of 18 months later with mean change in VA of +11 letters from baseline. In contrast, 176 eyes (23%) had a temporary suspension, they restarted therapy within 36 months, only to achieve mean change in VA of +7 letters at final review. We cannot accurately infer cessation of treatment in eyes that maintained suspension of therapy through final review but when combined with eyes that had discontinuation reasons suggesting cessation (9%, below), it was a group of similar size to those still requiring treatment (39%) at 3 years.

9.4.4 Non-completion of 36 Months

Outcomes in non-completers (289 [47%]) at final review were very similar to those of 36-month completers including the primary outcome of mean change in VA (95% CI) +11 letters (9, 13), mean final VA 68 letters and mean CST 311μm (Table 9.5). Non-completion rates differed significantly based on initial VEGF inhibitor (bevacizumab 44%, ranibizumab 41%, aflibercept 63%; $P < 0.001$, Figure 9.3A). The 63% of aflibercept eyes that non-completed did so with good outcomes at final review to suggest many may have concluded therapy including mean change in VA of +12 letters, mean VA of 70 letters and mean CST 285μm. Discontinuation reasons in all eyes were available in 68/344 (20%) non-completers, 15 transferred to another physician; cessation was implied (53 eyes) in 18 that had “treatment successful”, 11 “declined treatment”, 2 had “medical contraindications” and in 5 “further treatment was futile”, 17 patients died.

Figure 9.3. Kaplan-Meier Survival Curves of A) Non-completion and B) Switching.

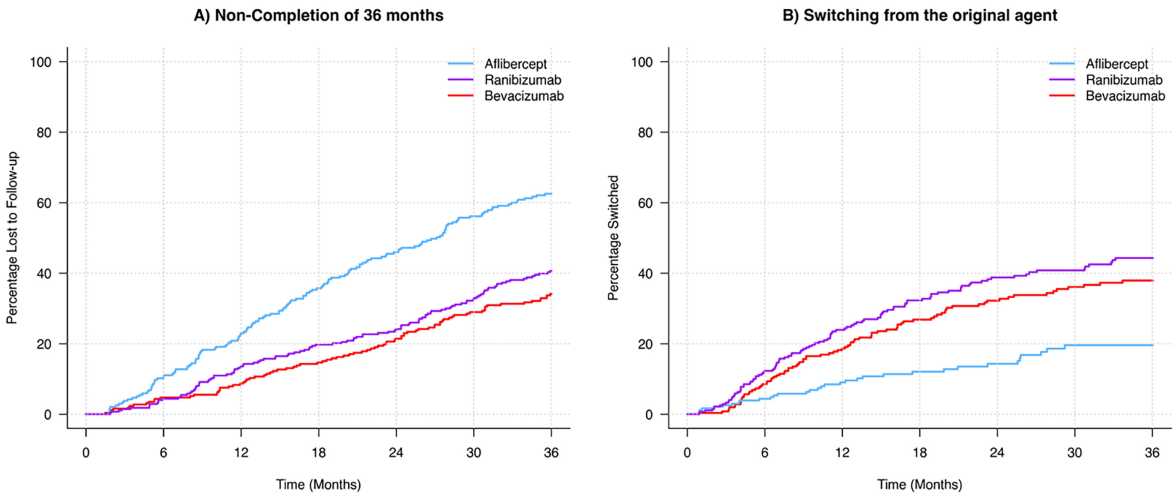


Table 9.5. Outcomes in Non-Completers Based on Treatment Received.

	All non-completers	*Monotherapy non-completers*	*VEGF-Switched Non-Completers*	*Steroid-Switched Non-Completers*
Eyes, n, (% entire cohort)	344 (45%)	282 (37%)	321 (42%)	23 (3%)
VA Baseline, mean (SD)	57 (18)	56 (19)	57 (19)	59 (8)
VA Final, mean (SD)	68 (19)	69 (18)	69 (18)	50 (25)
VA Change, mean (95% CI)	11 (9, 13)	13 (11, 15)	12 (10, 14)	-8 (-20, 3)
Gain ≥ 15 letters, %	40%	43%	41%	26%
Loss ≥ 15 letters, %	7%	4%	4%	39%
VA ≥ 70 %Baseline / %Final	30% / 62%	30% / 66%	31% / 64%	13% / 30%
VA ≤ 35 %Baseline / %Final	14% / 7%	16% / 6%	15% / 6%	0% / 26%
CST Baseline, mean (SD)	471 (157)	471 (150)	469 (152)	494 (216)
CST Final, mean (SD)	311 (116)	294 (94)	301 (98)	454 (222)
CST Change, mean (95% CI)	-160 (-180, -140)	-177 (-197, -157)	-169 (-188, -149)	-40 (-161, 82)
Injections, median (Q1, Q3)	7 (5, 11)	7 (4, 10)	7 (5, 11)	12 (8, 14)
Visits, median (Q1, Q3)	12 (8, 17)	11 (8, 15)	12 (8, 16)	19 (15, 26)
Suspension at final review, n (% column) *	77 (22%)	67 (24%)	74 (23%)	3 (13%)
Focal laser treatment, n (% column)	11 (3%)	8 (3%)	9 (3%)	2 (9%)
Sectoral Photocoagulation, n (% column)	43 (12%)	30 (11%)	38 (12%)	5 (22%)
Elevated IOP requiring treatment, n (% column)	2 (1%)	0 (0%)	1 (0%)	1 (4%)
Cataract surgery performed, n (% column)	15 (4%)	11 (4%)	12 (4%)	3 (13%)

All Eyes – outcomes without censoring observations after switching and using last observation carried forward in non-completers, Monotherapy – eyes treated with initial vascular endothelial growth factor inhibitor only, VEGF-Switched – ≥ 2 alternate VEGF injections, Steroid-Switched – ≥ 1 steroid injection. n – Number, VA – Visual Acuity, SD – Standard Deviation, CST – Central Subfield Thickness. Q1 – First Quartile, Q3 – Third Quartile, IOP – Intraocular pressure. * No treatment observed for >180 days leading up to final review

9.4.5 Switching

Switching occurred in 222/760 eyes (29%). Switching rates differed significantly based on initial VEGF inhibitor (bevacizumab 33%, ranibizumab 38%, aflibercept 14%; $P < 0.001$, Figure 9.3B). More than half of all switching was to aflibercept (121/760 [16%]). Aflibercept was the last injection given in 323/760 eyes (42%). Steroid switching was to the dexamethasone implant (73/760 [10%]) or triamcinolone (10/760 [1%]). Eyes that switched

to an alternate VEGF therapy (139/760 [18%]) had similar outcomes to non-switchers (Table 9.2) but received more injections (18 vs. 10; $P < 0.01$) and completed 3 years more often (72% vs. 55%; $P < 0.01$). Eyes that switched to steroid (83 [11%]) lost around 4 letters on average from baseline, had more cataract surgery (39% versus. 11%; $P < 0.01$) and more often started new therapy to control intraocular pressure (13% versus. 2%; $P < 0.01$) than eyes that did not receive steroids.

Table 9.6. Switching Outcomes at Time of Switch and Final Review.

Original VEGF group	*Switched between VEGF agents*			*Switched to a Steroid agent*	
	To: Bevacizumab	*To: Ranibizumab*	*To: Aflibercept*	*To: Triamcinolone*	*To: Dexamethasone*
Bevacizumab initially					
Eyes (% of original group)		23 (9%)	47 (19%)	9 (4%)	16 (6%)
VA Switch, mean (SD)		71 (11)	69 (12)	63 (15)	68 (9)
VA Final, mean (SD)		64 (22)	69 (15)	56 (25)	54 (29)
VA Change after Switch, mean (SD)		-6 (23)	0 (14)	-7 (25)	-14 (23)
CST Switch, mean (SD)		410 (118)	420 (124)	443 (102)	420 (151)
CST Final, mean (SD)		343 (124)	361 (114)	325 (83)	423 (161)
CST Change after Switch, mean (SD)		-67 (100)	-60 (147)	-118 (97)	3 (206)
Ranibizumab initially					
Eyes (% of original group)	9 (3%)		74 (27%)	1 (0%)	40 (15%)
VA Switch, mean (SD)	72 (10)		67 (18)	35 (NA)	63 (17)
VA Final, mean (SD)	68 (13)		66 (22)	85 (NA)	54 (23)
VA Change after Switch, mean (SD)	-4 (17)		-1 (19)	50 (NA)	-9 (22)
CST Switch, mean (SD)	312 (77)		383 (125)	238 (NA)	422 (124)
CST Final, mean (SD)	360 (111)		334 (126)	251 (NA)	381 (168)
CST Change after Switch, mean (SD)	49 (153)		-47 (161)	13 (NA)	-42 (164)
Aflibercept initially					
Eyes (% of original group)	3 (1%)	17 (7%)		0	17 (7%)
VA Switch, mean (SD)	61 (12)	57 (25)			53 (20)
VA Final, mean (SD)	66 (11)	58 (25)			57 (23)
VA Change after Switch, mean (SD)	6 (2)	1 (23)			4 (24)
CST Switch, mean (SD)	366 (87)	396 (143)			429 (175)
CST Final, mean (SD)	282 (8)	363 (186)			380 (209)
CST Change after Switch, mean (SD)	-84 (79)	-33 (180)			-49 (115)

VA = visual acuity in log MAR letters, CST = central subfield thickness in microns.

New macular changes were recorded more frequently in eyes that switched, including epiretinal membrane, macular hole, pigment change or atrophy (41/538 [8%] monotherapy

eyes, 24/139 [17%] alternate VEGF eyes, 24/83 [29%] steroid eyes; $P < 0.01$). Specific switching outcomes at time of switch and final review are described in Table 9.6.

9.4.6 Adverse outcomes

A total of 10142 injections were delivered in the study with three vitreous haemorrhages (mean final VA, 75 letters), one traumatic cataract (65 letters) and one case of infectious endophthalmitis (30 letters).

9.5 Discussion

This study describes an overall visual gain of +11 letters at 3 years with a median number of 16 injections and 24 visits in a multicentre international cohort of treatment naïve BRVO eyes treated in routine clinical care. The data described in this report extend the preliminary findings described in our previous 12 months outcomes analysis (Hunt et al., 2022; Wang et al., 2022), with marked visual gains during the loading dose maintained in the extension phase beyond the first year of treatment. The subgroup analysis by treatment drug is consistent with our previous findings, which revealed greater anatomical results for aflibercept compared to other compounds but no differences in visual outcomes. Additional findings are the treatment patterns observed favouring VEGF inhibitor monotherapy and the similar results observed in completers and non-completers, suggesting that the reasons for dropout in many eyes were likely because of disease resolution rather than lack of clinical response to VEGF inhibitors.

The visual results observed in this study are inferior to previous RCTs and consistent with previous RWD with shorter follow-up (Ang et al., 2020). We observed an overall VA gain of +11 letters at 3 years, which was observed with the loading dose and maintained thereafter, consistent with our previously reported 12-month data (Hunt et al., 2022). Interestingly, we report a relatively high number of injections, which may have avoided the risk of

undertreatment frequently reported by RWD. However, this 3-year gain is still lower than the BRAVO and HORIZON extension study results at 2 years (+17.5 letters) and VIBRANT at 1 year (+17.1 letters) (Campochiaro et al., 2010; Clark et al., 2016; Heier et al., 2012). The observed inferior gains in mean VA could be explained in part by the higher baseline mean VA of our study cohort (57 letters vs 53 letters) and our thinner mean CST (479 vs 551 microns) compared to BRAVO. Our cohort's baseline characteristics were similar to VIBRANT (58.6 letters and 558 microns) (Campochiaro et al., 2010; Clark et al., 2016). These results however are consistent with a recent Cochrane review that also pointed out that in BRVO the main visual gains with VEGF inhibitors were achieved at 6 months and then maintained at 12 months (Shalchi et al., 2020). Very few RCT and RWD studies have explored these outcomes beyond one year, the few that have reported 24 month outcomes had a very reduced number of eyes (Campochiaro et al., 2014; Chatziralli et al., 2018; Kornhauser et al., 2016; Ozkaya, Tarakcioglu, & Tanir, 2018; Tsagkataki, Papathomas, Lythgoe, & Kamal, 2015; Wu et al., 2008). In this report, we demonstrate that VEGF inhibitors are able to maintain these gains up to 3 years in routine clinical care.

One of the main objectives of our study was to provide specific details on how BRVO was managed over 3 years. We found a median number of 16/24 injections/visits over 3 years in completers. We report a higher number of injections compared to the RETAIN study (n=12.9 injections/3 years) (Campochiaro et al., 2014) and other RWD (5.9 and 6.8 injections/3 years), which could explain the positive results we found (Chatziralli et al., 2018; Farinha et al., 2015). Suspensions of therapy for 180 days during the 3-year study were observed in approximately half of the study cohort (44%, 331/760) and were sustained at the end of the follow-up in a quarter of these cases (26%, 198/760) with good outcomes (+11 letters, 63% > 70 letters). Relapses after a suspension were observed in approximately a quarter of the study eyes (176/760, 23%) with lower VA gain (+7 letters). A third of the cases were still receiving treatment at 3 years (296/760, 39%).

Most eyes studied received treatment exclusively with VEGF inhibitors (89%, n=677), including 71% that received monotherapy using the same agent throughout. Switching to a different VEGF inhibitor was found in 18% of eyes, most (84%) that switched did so to aflibercept, probably related to the greater anatomical response observed with this agent in our series. Very few eyes were switched to alternative therapies such as steroids (10%, n=83). This is relevant, as the switch to steroids frequently occurs early in the course of the disease (Yap et al., 2021) with very limited long-term data. The 136 (18%) eyes that received sectoral PRP received a similar number of injections as the overall cohort, suggesting that it does not exacerbate CME in eyes receiving intravitreal therapy for BRVO.

The three-year visual and anatomic outcomes of completers were very similar to non-completers, suggesting that some eyes may have discontinued treatment successfully. This is different from other conditions such as nAMD, where eyes that discontinue treatment commonly have worse outcomes. This may be explained by the different pathophysiology of the three conditions. As described in the original BVOS study, in some eyes with RVO the event may be self-limiting and may be reperfused with collateral vessels ("Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group," 1984) whereas AMD is a chronic condition. Similar to our report on 12-month BRVO outcomes, eyes starting with aflibercept achieved better anatomic outcomes through 36 months, even though VA gains were not significantly different between the agents. This may be explained again by the pathophysiology of BRVO, which predominantly affects the inner retinal layers and spares the outer retina, preserving the ability to maintain good levels of visual acuity even in eyes with an incomplete anatomical response.

This study has some limitations, beyond its observational design. We excluded hemiretinal vein occlusions, that have larger improvements in VA with VEGF inhibitors than BRVO in routine care (Hunt et al., 2022), unlike many of the previous RCT such as BRAVO, VIBRANT, or BRIGHTER which enrolled such patients. This is potentially another reason

why our real-world results are inferior to RCTs (Clark et al., 2016; Heier et al., 2012; Tadayoni et al., 2017). The treatment regimens were not homogeneous between centres, as is inevitable in a multicentre international case series where local policies are often directed by national regulatory bodies (i.e. drug agencies, national society´s recommendations, etc.) and individual practitioners may have their own unique approach. This is not necessarily a limitation as it reflects real world practice (Zarranz-Ventura, Nguyen, et al., 2022). We do not have full 3-year outcome data on approximately half the cohort, as the number of treatment interruptions (44%) and non-completers (47%) indicate, however the good final outcomes of non-completers suggest that many may have discontinued therapy successfully. Finally, the participating centres contributing data to the FRB! project may not reflect all retina practices, as its use represents the implementation of a measure of the quality of care that is not in place in all centres.

In conclusion, this report describes the 3-year visual and anatomical outcomes achieved with VEGF inhibitors in a large international multicentre study of eyes treated in routine clinical care, using a validated web-based registry for data collection. Our findings extend our published 12-month real world outcomes for BRVO, with the initial visual gains generally maintained for up to 3 years of follow-up. At least half of the eyes were still requiring treatment, but a significant number had been able to discontinue treatment with good vision.

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CHAPTER 10: CONCLUSIONS

Retinal Vein Occlusion (RVO) is associated with significant morbidity (Laouri, Chen, Looman, & Gallagher, 2011). Obstruction of the retinal venous system impairs visual acuity (VA), reduces quality of life and macular oedema requires frequent treatment involving eye injections that place significant burden on patients and care givers (Awdeh et al., 2010; Deramo, Cox, Syed, Lee, & Fekrat, 2003; Fekrat et al., 2010).

The Fight Retinal Blindness! (FRB!) registry was established in 2008 with the aim of monitoring and optimising outcomes of intravitreal therapy in retinal disease (Gillies et al., 2014). Modules collecting a prospectively designed minimum outcomes dataset specifically for nAMD (2008), DMO (2009) and RVO (2011) were rolled out gradually. The FRB! registry has steadily grown to become one of the most advanced ophthalmic registries in the world. The strength of FRB! lies in the collection of trial-like data from the real-world setting. The datasets are lean yet powerful.

The primary motivation for this thesis was to harness the power of the FRB! registry to help improve the real-world evidence supporting the treatment of patients with RVO using VEGF inhibitors in routine care. When planning the project, patients with neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DMO) were much better served by the quality of observational research supporting their management than patients with RVO. Many scientifically robust real-world studies regarding intravitreal therapy for nAMD and DMO had been generated by the Fight Retinal Blindness! (FRB!) project but RVO was least studied (Nguyen, Barthelmes, & Gillies, 2021). The analysis of FRB! data has led to quality research outputs upon which this thesis has added a foundation for future work (https://savesightregistries.org/research-outputs/).

The first aims of this thesis were to compare 12-month real-world treatment outcomes of aflibercept and ranibizumab in separate analyses of treatment-naïve eyes with central retinal vein occlusion (CRVO) and with branch retinal vein occlusion (BRVO). Existing evidence

had only compared these agents in select cohorts with predominantly CRVO, finding them non-inferior (Hykin et al., 2021; Narayanan et al., 2016; Rajagopal et al., 2015; Scott et al., 2017; Vader et al., 2020).

Our studies included broad cohorts of CRVO and BRVO and found that aflibercept was superior to ranibizumab in improving visual acuity for patients with CRVO and in reducing macular thickness for patients with either BRVO or CRVO managed in routine care. It is possible that the relative efficacy of the agents was borne out by comparisons being made in more representative cohorts exposed to relative undertreatment typical of routine care. The third part of the project described the 12-month outcomes using “off-label” bevacizumab in RVO, the most frequently used agent in New Zealand.

The variable inclusion of eyes with hemi-retinal vein occlusion (HRVO) within trial cohorts of either BRVO or CRVO was noted in the review if the literature. An analysis focussing on HRVO was needed to determine whether this practice was justified. It found that HRVO generally performed better than other subtypes when treated with VEGF inhibitors in routine care through 12 months. The visual acuity (VA) and central subfield thickness (CST) in eyes with HRVO uniquely started more like CRVO but ended more like BRVO. This raises questions regarding the validity of including eyes with HRVO in BRVO or CRVO study cohorts.

When VEGF inhibitors first started to be used for RVO the plan was to protect patients from the detrimental effects of chronic macular oedema (MO) until they no longer needed treatment. We knew from natural history studies that the pathology in RVO may eventually resolve either through recanalisation of the occlusion or through the development of collaterals (Chopdar, 1982; Green, Chan, Hutchins, & Terry, 1981; McAllister & Barry, 1991). This was good in theory but with experience it was apparent many patients with RVO required ongoing treatment to maintain outcomes. Trials spanning 12-24 months certainly

supported commencement of therapy, but a paucity of evidence informed management beyond that period.

The next aims of the thesis were to improve longer-term prognostication for treatment-naïve patients with CRVO or BRVO commencing bevacizumab, ranibizumab or aflibercept. Little insight could be gleaned from existing real-world evidence that lacked reasonable follow-up or described outcomes in “completers-only” (Chatziralli et al., 2018; de Salles & Epstein, 2021; Farinha et al., 2015; Spooner, Fraser-Bell, Hong, & Chang, 2019; Wu et al., 2022). In separate BRVO and CRVO 36-month analyses we accounted for outcomes in completers (+11 and +12 letters) and non-completers (+11 and +7 letters), outcomes were also predicted using models for the entire cohort had they all continued follow-up through 36 months (+10 to +11 letters). We found the choice of VEGF inhibitor had little impact on visual outcomes at 36 months even though the superiority of aflibercept in reducing macular thickness continued through 36 months in eyes with either BRVO or CRVO.

The analyses of the 36-month outcomes of BRVO and CRVO provided some answers to questions most often asked by patients with RVO wanting to know what to expect from treatment. In simple terms, we found three years after starting VEGF inhibitors in routine care that one-third of eyes with CRVO had good vision (≥ 6/12) and one-third poor vision (≤ 6/60). In BRVO, two-thirds had good vision and very few had poor vision. Eyes in our studies in the 1st, 2nd and 3rd year received around 8, 5 and 4 injections and half of all eyes with RVO still required injections 3 years after starting them.

An overarching principle of this thesis was inclusivity of one patient after another starting treatment for RVO using VEGF inhibitors in routine practice. For example, the requirement in trials for eyes with CRVO to have baseline VA between 19-73 letters meant that outcomes were not accounted for in many eyes including those with ischaemia (Brown et al., 2010; Brown et al., 2013; Hykin et al., 2019; Korobelnik et al., 2014; Larsen et al., 2018; Scott et

al., 2017). In our 36-month CRVO analysis, 24% of eyes presented with very poor baseline VA (< 19 letters) but had the largest gains (+22 letters) while 8% with very good baseline VA (> 73 letters) lost VA (-7 letters). This shows the impact of baseline VA on individual outcomes and the impact of excluding these eyes from studies. Eyes in our study with CRVO and trial-eligible baseline VA (19-73 letters) had less impressive gains of +7 letters compared with the overall cohort (+11 letters) at 36 months.

A common theme in real-world clinical practice is undertreatment. It was not as severe in our broad cohorts as it was in many studies discussed in the literature review, but it was still apparent compared with clinical trials. The effects of undertreatment were offset to some degree by including such a broad cohort with CRVO. Overall outcomes for eyes with CRVO were boosted by the inclusion of one quarter with very baseline poor vision (< 19 letters) that had large improvements in VA (+22 letters at 3 years). Perhaps the approval of agents with greater efficacy and durability will help bridge the gap between outcomes achieved in routine care and those reported in trials. The FRB! RVO module will track outcomes of these emerging therapies as they are released (Tadayoni et al., 2024). Nevertheless, the analysis of large volumes of high-quality observational data regarding treatment outcomes using first generation VEGF inhibitors that are presented in this thesis will likely provide relevant insights in the treatment of RVO irrespective of the agent delivered in the future.

This research has several limitations inherent to observational studies. Treatment decisions in routine clinical practice were at the discretion of the treating physician and clinical findings were not corroborated by reading centres like they are clinical trials. The inclusion of consecutive patients cannot be guaranteed however participating physicians do agree to enter at least 85% of their patients that would be eligible to be tracked. Limitations specific to each manuscript are in Chapters 4 to 9.

The research reported in this thesis provides a foundation for future work. The lower treatment intensity of patients with RVO in routine care compared with trial patients appeared to have the greatest impact on outcomes in eyes with CRVO. Aflibercept had greater efficacy than ranibizumab in reducing macular thickness in BRVO and CRVO and improving visual acuity in CRVO in routine care. Particularly good outcomes in eyes with HRVO when treated with VEGF inhibitors in routine care suggest caution should be exercised when including them in BRVO or CRVO cohorts to avoid skewing results. The outcomes in eyes with BRVO and CRVO treated with VEGF inhibitors in routine care were largely maintained through 3 years, but half of eyes still required injections. The initial choice of VEGF inhibitor no longer significantly influenced visual outcomes after 3 years though aflibercept continued to be more efficacious in reducing macular thickness. Ongoing research in this field is warranted to analyse the outcomes of new agents for RVO that may last longer, thereby reducing treatment burden and possibly reducing the detrimental effect of undertreatment in routine care. A study that helps identify which eyes can successfully attempt cessation of VEGF inhibitors in RVO is needed, as are studies describing longer-term outcomes of treatment of RVO through 5 years.

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APPENDIX I: FRB! and Consent Form

PRACTICE LOGO
CONTACT DETAILS
Name: (Your Doctor)
Address:
Telephone: Fax:
Name: (Practice Contact)

Patient Information Sheet

Your practice name

Save Sight Registries
Seeing Outcomes

WHO SHOULD I CONTACT IF I HAVE CONCERNS ABOUT CONDUCT OF THIS PROJECT?

This project has been approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (SESLHD) and The Royal Australian and New Zealand College of Ophthalmologists Ethics Committee (RANZCO). Any person with concerns or complaints about the conduct of this study should contact:
SESLHD – quote HREC Ref number 13/037 on 02 9382 3587 or email ethicsnhn@sesiahs.health.nsw.gov.au; or RANZCO – quote HREC Ref number 09/73 on 02 9690 1001 or email ranzco@ranzco.edu

If you do not wish your data to be used in this manner please tick the box below and advise our staff accordingly.

☐ **I do not wish my clinical or personal data (year of birth, gender, ethnicity or postcode) to be included in this research or audit activity conducted at this practice.**

Name: .....

Signature: ..... **Date:** .....

This practice is participating in a research project called **Fight Retinal Blindness!** conducted by the University of Sydney.

This registry tracks the outcomes of treatments for eye conditions including neovascular ("wet") age-related macular degeneration (nAMD), Diabetic Macular Edema (DME) and Retinal Vein Occlusion (RVO). All of these conditions may be treated by injection of drugs into the eye. This project looks at the different ways in which doctors use these treatments to find out which way gets the best outcomes for patients.

AMD causes vision to be lost either from a slow atrophic process (dry AMD) or in a much more rapid and destructive way (wet AMD) where new blood vessels invade and destroy the degenerating macula. Around 1 in 7 Australians over the age of 50 (1 million Australians) have some early signs of AMD.

Diabetic Retinopathy (damage to the blood vessels in the retina) is caused by complications of diabetes which can eventually lead to blindness. Diabetic retinopathy has been reported to be the leading cause of blindness in people aged 30–69 years and approximately 1 in 4 people with diabetes will be affected by it.

Retinal Vein Occlusion (RVO) is when one of the veins in the retina becomes blocked. It may lead to varying degrees of vision loss, depending on the severity and location of the blockage. It affects about 1 to 2% of people over 40, although most cases occur in people over 60.

PURPOSE OF THE PROJECT
The purpose of the project is to record information about how these conditions are managed using both existing and new treatments. We will develop guidelines for eye doctors to help them provide the best management for their patients. We will also use the results to determine whether the new treatments are safe and effective in every day clinical practice.

HOW DOES THIS AFFECT ME?
You will see the eye doctor you usually see and that doctor will look after your eyes the way he or she thinks is best. You are not required to do anything other than what your eye doctor suggests. We will not tell your doctor how to treat you. Your information will always be non-identifiable so we will not be able to identify you. The only personal information collected is: year of birth, gender, ethnicity and postcode to determine if any of these variables affect outcomes. The medical information we need includes the results of your examination and vision tests and any related treatment you might have, and whether you have any bad reaction to the treatment.

We will combine this information with information about how other people are treated. They may be treated the same as you, or differently to you. We may also ask you to complete a questionnaire on your vision and general well-being. The questionnaire will tell us, and your doctor, what you think about your vision. You may be asked to do the questionnaire each year during your treatment. This will enable your doctor to understand better how your vision impairment is affecting your daily life.

RISKS
There are no risks other than those usually associated with the condition that you are seeing your eye doctor for.

WILL YOUR DOCTOR BE PAID?
None of the clinicians are being paid to undertake this activity, they participate to better understand how effective certain treatments are.

DATA COLLECTION, STORAGE, USE AND DISPOSAL
We will not record the names of patients. All information collected is coded so that you cannot be identified. This non-identifiable data is collected by a secure web-based system, encrypted, transmitted and stored in a secure server at the University of Sydney's Information and Communication Technology (ICT) Department. The database is only accessible by doctors' personal logins. The ability to access his/her data enables the doctor to evaluate his/her treatments on each patient. The data collected by your doctor can then be used for performance benchmarking so that doctors can compare their results with those of other doctors using the system.

PUBLISHING OUR FINDINGS
Any findings, including guidelines for eye doctors, will be published in major scientific journals and presented at conferences such as the annual Royal Australian and New Zealand College of Ophthalmologists Congress.

SUPPORT FOR THE PROJECT
Save Sight Registries activities rely on fundraising to achieve its objectives. Our funding comes from a variety of sources including, RANZCO, Eye Foundation; National Health and Medical Research Council; Donations; Bequests; Pharmaceutical and Technology companies (Novartis, Bayer, Glaukos)

For further information visit **www.savesightregistries.org**

APPENDIX II: LogMAR VA Conversion

VISUAL ACUITY - LogMAR conversion

	SNELLEN READING	SNELLEN DECIMAL	Equivalent # of letters read on chart	ENTER THIS SCORE LogMAR Score
*	No Light Perception (6/300)	0.02		0
*	Perceives Light (6/240-4)	0.0209		1
*	Hand Movements (6/240-3)	0.0219		2
*	Count Fingers (6/240-2)	0.0229		3
	6/240 (1.5/60)	0.025		5
	2/60	0.03		10
	6/120 (3/60)	0.05		20
	4/60	0.06		25
	5/60	0.08		30
	6/60	0.1	5	35
	6/48	0.125	10	40
	6/38	0.16	15	45
	6/30	0.2	20	50
	6/24	0.25	25	55
	6/19	0.3	30	60
	6/15	0.4	35	65
	6/12	0.5	40	70
	6/9.5	0.6	45	75
	6/9	0.67	48	76
	6/7.5	0.8	50	80
	6/7	0.86	53	82
	6/6	1.0	55	85
	6/4.8	1.25	60	90
	6/3.8	1.6	65	95
	6/3	2.0	70	100

Enter the Snellen equivalent score as shown in the right-hand column. Scores can be calculated where necessary i.e. 6/15-2 = 35 - 2 + 30 = 63

*The values for these fields are arbitrary.

APPENDIX III: Conference Proceedings

Hunt A, Nguyen V, Bhandari S, Ponsioen T, McAllister IL, Arnold J, Young S, Gabrielle PH, Mehta H, O' Toole L, Alforja S, Zarranz-Ventura J, Barthelmes D, Gillies M. **Central Retinal Vein Occlusion 36-Month Outcomes with Anti-VEGF: The Fight Retinal Blindness! Registry.**

Hunt A: Oral presentation to the Association for Research in Vision and Ophthalmology Annual Meeting ARVO 2022, 1-6 May in Denver, USA.

ARVO 2022

View Abstract

CONTROL ID: 3712857
SUBMISSION ROLE: Abstract Submission

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Commercial Relationships Disclosure: Adrian Hunt: Commercial Relationship: Code N (No Commercial Relationship) | Vuong Nguyen: Commercial Relationship: Code N (No Commercial Relationship) | Sanjeeb Bhandari: Commercial Relationship: Code N (No Commercial Relationship) | Jennifer J Arnold: Commercial Relationship(s):Code C (Consultant/Contractor):Novartis;Code C (Consultant/Contractor):Bayer;Code C (Consultant/Contractor):Allergan | Ian McAllister: Commercial Relationship(s):Code C (Consultant/Contractor):Novartis;Code C (Consultant/Contractor):Bayer | Hemal Mehta: Commercial Relationship: Code N (No Commercial Relationship) | Alessandro Invernizzi: Commercial Relationship: Code N (No Commercial Relationship) | David Squirrell: Commercial Relationship: Code N (No Commercial Relationship) | Theodorus Ponsioen: Commercial Relationship: Code N (No Commercial Relationship) | Pierre-Henry GABRIELLE: Commercial Relationship: Code N (No Commercial Relationship) | Louise O' Toole: Commercial Relationship: Code N (No Commercial Relationship) | Javier Zarranz-Ventura: Commercial Relationship: Code N (No Commercial Relationship) | Daniel Barthelmes: Commercial Relationship(s):Code F (Financial Support):Novartis | Mark Gillies: Commercial Relationship(s):Code C (Consultant/Contractor):Bayer;Code C (Consultant/Contractor):Allergan;Code C (Consultant/Contractor):Novartis

Study Group: Fight Retinal Blindness! Registry

ABSTRACT

TITLE: 36-month outcomes of VEGF inhibitors for treatment-naïve Central Retinal Vein Occlusion: Data from the Fight Retinal Blindness! registry.

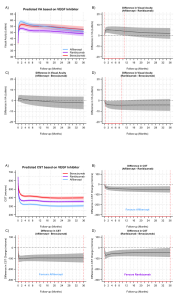
ABSTRACT BODY:

Purpose: We performed a retrospective analysis of a large prospectively specified observational database of patients with central retinal vein occlusion (CRVO) treated with vascular endothelial growth factor (VEGF) inhibition from routine practice.

Methods: We identified 527 treatment-naïve patients with CRVO that commenced VEGF inhibitors between January 1, 2010-2018, with a mean (SD) age of 71 years (12), visual acuity (VA) of 41 letters (25). The primary outcome was mean change in VA from baseline to 36 months. Adjusted VA and central subfield thickness (CST) outcomes compared VEGF agents with generalised mixed effects models.

Results: In all eyes, mean VA change (95% CI) was +10 (7, 12) letters, 44% gained and 14% lost ≥15 letters, 37% had final VA ≥70 and 30% ≤35 letters. Mean CST change was -306µm. The adjusted mean VA change was similar with each VEGF inhibitor (+12 letters) despite significant difference in adjusted mean CST change with aflibercept (-310µm), ranibizumab (-258µm) or bevacizumab (-216µm; $P < 0.001$). VEGF switchers (19%) gained +11 letters like non-switchers (69%) but with more injections (20 vs. 10; $P < 0.001$). Eyes that were switched to steroid (12%) had lower mean baseline VA 38 letters, 46% had final VA ≤35 letters and no mean change in VA from baseline. Mean VA change in eyes with *trial-eligible* baseline VA (19-73 letters, 356/527, 68%) was +7 letters. Eyes outside this range with *very-poor* baseline VA (<19 letters, 129/527, 24%) gained +22 letters and eyes with *very-good* baseline VA (>73 letters, 42/527, 8%) lost vision by -7 letters. Completers (257/527, 49%) had a median of 18 injections over 26 visits. Suspension of therapy >180 days occurred in 141/527 (27%) eyes but only 62 (12%) eyes had no macular oedema during that time. Treatment status was known in 356/527 (68%) eyes – 55% were still receiving injections at 3 years while 45% had suspended therapy.

Conclusions: Patients with CRVO that commenced VEGF inhibitors in routine care had VA improvements of around 10 letters at three years - almost matching the outcomes of extension studies that followed RCTs. The choice of VEGF inhibitor influenced CST but not VA outcomes. Half of all eyes were still being treated at 36-months.



Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.: Two line improvements in vision are typical with eye injections for central retinal vein occlusion, the choice of drug has little effect and half of all patients still require treatment at 3 years.

DETAILS

PRESENTATION TYPE: #1 Paper, #2 Poster
CURRENT REVIEWING CODE: 1700 Retinal vascular diseases (excluding diabetic retinopathy) - RE
CURRENT SECTION: Retina
Clinical Trial Registration (Abstract): No
Other Registry Site (Abstract): (none)
Registration Number (Abstract): (none)
Date Trial was Registered (MM/DD/YYYY) (Abstract): (none)

Hunt A, Nguyen V, Bhandari S, Ponsioen T, McAllister IL, Arnold J, Young S, Gabrielle PH, Mehta H, O' Toole L, Alforja S, Zarranz-Ventura J, Barthelmes D, Gillies M. **Central Retinal Vein Occlusion 36-Month Outcomes with Anti-VEGF: The Fight Retinal Blindness! Registry.**

Hunt A: Oral presentation to the Annual Scientific Congress of the Royal Australian and New Zealand College of Ophthalmologists, Brisbane, Australia, Oct 28 - 1 Nov 2022. Awarded Australian Vision Research recommended abstract.

RANZCO 2022
28 OCT - 1 NOV 2022
BRISBANE

Australian Vision Research recommended abstract

53rd Annual Scientific Congress 2022

Dr Adrian Hunt

Oral Program - **Retina**
36-month outcomes after starting VEGF inhibitors for treatment-naïve Central Retinal Vein Occlusion: Data from the Fight Retinal Blindness! registry.

Prof Stephanie Watson
Chair, Australian Vision Research

AUSTRALIAN VISION RESEARCH
australianvisionresearch.org

Hunt AR, Nguyen V, Arnold JJ, McAllister IL, Mehta H, Invernizzi A, Ponsioen T, Gabrielle PH, O'Toole L, Kusenda P, Alforja S, Barthelmes D, Gillies MC. **Hemiretinal vein occlusion 12-month outcomes are unique with vascular endothelial growth factor inhibitors: data from the Fight Retinal Blindness! Registry.**

Hunt A: Oral presentation to the European Society of Retinal Specialists Annual Meeting EURETINA Hamburg, Germany 2nd November 2022.

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.

Hunt AR, Nguyen V, Creuzot-Garcher CP, Alforja S, Gabrielle PH, Zarranz-Ventura J, Guillemin M, Fraser-Bell S, Casaroli Marano RP, Arnold J, McAllister IL, O'Toole L, Gillies MC, Barthelmes D, Mehta H. **Twelve-month outcomes of ranibizumab versus aflibercept for macular oedema in branch retinal vein occlusion: data from the FRB! registry.**

Hunt A: Oral presentation to the European Society of Retinal Specialists Annual Meeting EURETINA *Virtual* September 10th, 2021.

FREE PAPER TITLE (MAX 250 CHARACTERS)	Twelve-month outcomes of ranibizumab versus aflibercept for macular oedema in branch retinal vein occlusion: data from the FRB! registry
PURPOSE (MAX 500 WORDS)	To compare the efficacy of ranibizumab (0.5mg) to aflibercept (2mg) in the treatment of cystoid macular oedema (CMO) due to branch retinal vein occlusion (BRVO) over 12 months in a real-world setting.
SETTING/VENUE (MAX 250 WORDS)	A multicentre, international, database observational study recruited 322 eyes initiating therapy in real-world practice over 5 years utilising data from the Fight Retinal Blindness registry.
METHODS (MAX 500 WORDS)	The main outcome measure was mean change in EDTRS letter scores of visual acuity (VA). Secondary outcomes included anatomic outcomes, percentage of eyes with VA > 6/12 (70 letters), number of injections and visits, time to first inactivity, switching or non-completion.
RESULTS (MAX 500 WORDS)	Generalised mixed effect models demonstrated that mean (95% CI) adjusted 12-month VA changes for ranibizumab and aflibercept were similar (+10.8 [8.2, 13.4] versus +10.9 [8.3, 13.5] letters respectively, p = 0.59). The mean adjusted change in central subfield thickness (CST) was greater for aflibercept than ranibizumab (-170 [-153, -187] µm versus -147 [-130, -164] µm respectively, p = 0.001). The overall median (Q1, Q3) of 7 (4, 8) injections and 9 (7, 11) visits was similar between treatment groups. First grading of inactivity occurred sooner with aflibercept (p = 0.01). Switching was more common from ranibizumab (37 eyes, 23%) than from aflibercept (17 eyes, 11%; p = 0.002).
CONCLUSIONS (MAX 500 WORDS)	Visual outcomes at 12 months in this direct comparison of ranibizumab and aflibercept for BRVO in real world practice were generally good and similar for the 2 drugs, despite a greater effect of aflibercept on CST and time to first grading of inactivity.
THEME (CHOOSE ONE)	Vascular Diseases and Diabetic Retinopathy

APPENDIX IV: Included Publications

Acta Ophthalmologica

Acta Ophthalmologica 2021

12-month outcomes of ranibizumab versus aflibercept for macular oedema in central retinal vein occlusion: data from the FRB! registry

Mateusz Niedzwiecki,[1] Adrian Hunt,[2,3] Vuong Nguyen,[3] Hemal Mehta,[3,4] Catherine Creuzot-Garcher,[5] Pierre-Henry Gabrielle,[3,5] Martin Guillemin,[5] Samantha Fraser-Bell,[3] Jennifer Arnold,[6] Ian L. McAllister,[7] Mark Gillies[3] and Daniel Barthelmes[1,3]

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ABSTRACT.

Purpose: **To compare 12-month treatment outcomes of eyes receiving aflibercept or ranibizumab for macular oedema secondary to central retinal vein occlusion (CRVO) in routine clinical practice.**

Methods: **296 treatment-naïve eyes receiving either aflibercept (171 eyes, 2 mg) or ranibizumab (125 eyes, 0.5 mg) for macular oedema secondary to CRVO were recruited retrospectively from centres using the prospectively designed FRB! registry. The primary outcome measure was the mean change in LogMAR letter scores of visual acuity (VA). Secondary outcomes included change in central subfield thickness (CST), injections and visits, time to first grading of inactivity, switching and non-completion from baseline to 12 months.**

Results: **Baseline VA (SD) was somewhat better in aflibercept- versus ranibizumab-treated eyes (42.5 ± 25.5 letters versus 36.9 ± 26 letters; p = 0.07) with similar CST (614 (240) µm versus 616 (234) µm: p = 0.95). The 12-month adjusted mean (95%CI) VA change was +16.6 (12.9, 20.4) letters for aflibercept versus +9.8 (5.5, 14.1) letters for ranibizumab (p = 0.001). The mean (95%CI) adjusted change in CST was significantly greater in aflibercept- versus ranibizumab-treated eyes: −304 (−276, −333) µm versus −252 (−220, −282) µm (p < 0.001). Both groups had a median (Q1, Q3) of 7 (5, 9) injections and 10 (8,13) visits. Aflibercept-treated eyes became inactive sooner than ranibizumab (p = 0.02). Switching occurred more commonly from ranibizumab (26 eyes, 21%) than from aflibercept (9 eyes, 5%) (p < 0.001).**

Conclusion: **Both aflibercept and ranibizumab improved VA and reduced CST in eyes with CRVO in routine clinical practice, with aflibercept showing significantly greater improvements in this comparative analysis.**

Key words: aflibercept – CRVO – cystoid – macula – oedema – ranibizumab

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Introduction

Treatment of central retinal vein occlusion (CRVO) has progressed from prevention of sight-threatening sequelae (Hayreh 2003) to vascular endothelial growth factor (VEGF) inhibitors, which randomized controlled trials (RCTs) suggest can improved vision significantly (Campochiaro et al. 2011; Boyer et al. 2012; Brown et al. 2013; Korobelnik et al. 2014). There are, however, limited data showing that these impressive RCT outcomes are being achieved in routine clinical care and whether the licenced drugs, aflibercept and ranibizumab, are equivalent in the general population.

Randomized controlled trials (RCTs) mandate frequent intravitreal injections that pose a significant treatment burden which is difficult to always achieve in routine clinical practice (Kiss et al. 2014; Lotery & Regnier 2015; Stallworth et al. 2020). Various retrospective observational analyses suggest that fewer injections are given in the first 12 months than in RCTs, with correspondingly lower visual acuity gains (Chatziralli et al. 2017, 2018; Kitagawa et al. 2018; Callizo et al. 2019). On average, 4–5 injections were given in the first 12 months, resulting in an average visual gain of approximately 1.2 lines (Lotery & Regnier

2015; Gale et al. 2020; Stallworth et al. 2020).

The LEAVO study was a randomized clinical trial that reported that ranibizumab was non-inferior to aflibercept in CRVO (Hykin et al. 2019). There were selected cohorts treated under controlled conditions following a strict induction protocol followed by a PRN regimen from week 16 to week 96, which may be similar to routine clinical care. The VA outcomes at 12 months were similar between aflibercept- and ranibizumab-treated eyes (Hykin et al. 2019). The SCORE2 study reported that bevacizumab was 'non-inferior' to aflibercept in a heterogeneous group of eyes with CRVO or HRVO (Scott et al. 2017).

The quality of data from routine clinical practice is variable. 'Mining' large data sets from electronic medical records currently produces lower quality data, such as a recent report using data from the US Retina database, where baseline visual acuity could not be identified in 130 25 of 301 06 (35%) of eyes receiving anti-VEGF treatment for age-related macular degeneration (Kiss et al. 2020). Outcomes registries with prespecified mandatory fields – such as the Fight Retinal Blindness! Project – require users to enter all data within prespecified ranges for the visit to be 'finalized' and accepted into the database. Finalization rates consistently exceed 95% of recorded visits. The additional effort users make produces higher quality, complete data sets.

Here, we report a comparative analysis of 12-month treatment outcomes of a large cohort of patients in routine clinical practice who received aflibercept or ranibizumab for macular oedema secondary to CRVO from participating centres in the Fight Retinal Blindness! Project.

Materials and Methods

Design and setting

We conducted a retrospective analysis of eyes with CRVO treated with approved intravitreal anti-VEGF agents. Treatment was tracked in routine clinical practice within the prospectively designed retinal vein occlusion module of the Fight Retinal Blindness! Registry (Gillies et al. 2014). Participants were treatment-naïve and managed at clinics in Australia, France, Switzerland and the United Kingdom. Ethics and data protection approval was obtained from the University of Sydney and the Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09), the French Institutional Review Board (2017_CLER-IRB_ll-05), the Cantonal Ethics Commission in Zurich (PB_2016-00264) and the Caldicott Guardian of the Royal Free London NHS Foundation Trust (Dr Kilian Hynes). The study adhered to the STROBE checklists for reporting observational studies (von Elm et al. 2008) and followed the tenets of the Declaration of Helsinki. All patients gave informed consent. An 'opt-in' informed consent was sought from patients from France, Switzerland and the United Kingdom. An 'opt-out' patient consent was approved by Ethics committees in Australia.

Data sources and measurements

Data were collected at each clinical visit including the number of letters read on a logarithm of the minimum angle of resolution (logMAR) VA Chart (highest of uncorrected, corrected or pinhole), the activity (presence of intraretinal cystoid changes) of cystoid macular oedema (CME [yes/no]), the central subfield thickness (CST [μm]) measured using spectral-domain optical coherence tomography (OCT), treatment given, other ocular procedures and ocular adverse events. Relevant systemic risk factors or ocular conditions were recorded at baseline only, as was the type of RVO (CRVO, hemi-RVO or branch-RVO) (McAllister et al. 2014), and if a fluorescein angiogram was performed, whether macular or peripheral ischaemia was documented. Drug choice and treatment frequency were at the physician's discretion in consultation with the patient reflecting routine clinical practice.

Patient selection

Treatment-naïve eyes that started treatment with either ranibizumab (0.5 mg Lucentis, Genentech Inc/Novartis) or aflibercept (2 mg Eylea, Bayer) from 1 June 2014 to 1 June 2019 were studied. Eyes with hemi-RVO or branch-RVO were excluded. Eyes that had at least three visits and were followed for 12 months were defined as 'completers'. Switchers were defined as eyes that received ≥2 injections of the other drug prior to switching. Visits occurring after the switch were not included in this analysis. Eyes that did not complete 12 months of observations were defined as 'non-completers'.

Outcomes

The main outcome was the mean change in VA at 12 months between anti-VEGF agents. Secondary outcomes were the mean change in CST, number of visits and the number of injections. Other event-based outcomes of interest were first grading of CME inactivity, switching and non-completion rates over 12 months.

Statistical analysis

Descriptive data were summarized using the mean, standard deviation, median, first and third quartiles, and percentages where appropriate. Eyes were observed from the first treatment visit to their 12-month (365 ± 30 days) visit. T-tests, Wilcoxon signed-rank tests, chi-square tests and Fisher's exact tests were used as appropriate to compare baseline characteristics between ranibizumab- and aflibercept-treated eyes. Calculation of crude visual and anatomic outcomes at 12 months used the last observation carried forward (LOCF) for switchers and non-completers. We used longitudinal generalized additive mixed-effects models to compare VA and CST outcomes between the treatments over the 12-month period with the interaction between injection group and time as the main predictor. The longitudinal models included all visits up until 12 months from completers, non-completers and switchers without imputation of missing data (i.e. LOCF). Visits occurring after an eye switched drugs were not included. We adjusted for age and baseline VA or CST as fixed effects, and nesting of outcomes within doctor and patient (for bilateral cases) as random effects. We used predictions from these models to plot predicted VA and CST, and the difference in the mean predicted VA and CST, over 12 months for each drug.

Generalized Poisson linear mixed models were used to compare visits and injections with an offset for log days of follow-up. Kaplan–Meier survival analysis was used to assess the time to first grading of CMO inactivity,

non-completion and switching. A Cox-proportional hazards model was used to compare time to inactivity between treatment groups. Generalized Poisson and Cox-proportional hazards models were adjusted for age, baseline VA and baseline CST as fixed effects, and nesting of outcomes within doctor and patient as random effects.

All analyses were conducted using R version 4.0.0 (http://www.R-project.org/) using the *glmmTMB* (V1.0.1) package for generalized linear mixed-effects regression, the *mgcv* (V1.8-31) package for generalized additive mixed models and the *coxme* (V2.2-16) and *survival* (V3.1-12) packages for time-to-event analyses (R Core Team 2020).

Results

Study participants

We identified 296 treatment-naïve patient eyes (125 ranibizumab and 171 aflibercept) in 291 patients with cystoid macular oedema secondary to CRVO that started treatment with either ranibizumab or aflibercept from 1 June 2014 to 1 June 2019 (Table 1).

There were no statistically significant differences at baseline in eyes grouped by VEGF inhibitor. Eyes receiving ranibizumab were slightly older (73 versus 71 years; p = 0.14), had lower mean baseline visual acuity (36.9 versus 42.5 letters; p = 0.07), more presented with VA ≤ 35 letters (45% versus 38%, p = 0.29) and were less likely to have a history of systemic hypertension and glaucoma than those receiving aflibercept. The groups had very similar mean (SD) baseline CST (ranibizumab 614 (240) μm versus aflibercept 616 (234) μm; p = 0.95). Fundus fluorescein angiography (FFA) was performed in 60% of all eyes studied. Twenty eyes overall that had documented macular ischaemia were more likely to have baseline visual acuity ≤35 letters (p = 0.01); however, the treatment groups had no significant difference in documented ischaemia at baseline including both macular (7%) and peripheral ischaemia (25%).

Visual outcomes at 12 months

Mean crude VA improvement (95% confidence interval [CI]) was higher for aflibercept than for ranibizumab (+13.1 letters [9.4, 16.8] versus +9.9 [5.8, 14.1] (p = 0.26), including eyes that switched or dropped out (using LOCF) (Table 2).

This trend was more pronounced in eyes presenting with baseline VA ≤ 35 letters (38% in the aflibercept-treated group and 45% in the ranibizumab-treated group) with mean crude VA improvement in the aflibercept group of +24.6 (18.5, 30.7) letters versus +16.6 (10.4, 22.8) letters in the ranibizumab group (p = 0.07) from similar mean baseline VA: 13.7 (13.7) letters versus 11.9 (13.2) letters (p = 0.46) (Table S1). The treatment groups started with very similar proportions of eyes with VA ≥ 70 at baseline (13%); however, more eyes in the aflibercept group (42%) had VA ≥ 70 letters at 12 months than in the ranibizumab group (30%; p = 0.05).

The generalized additive mixed model (*Methods*) predicted a mean adjusted VA change (95% CI) that was greater with aflibercept +16.6 (12.9, 20.4) letters than +9.8 (5.5, 14.1) letters with ranibizumab group (p = 0.001). The mean adjusted VA over 12 months for each group is shown in Fig. 1A, while Fig. 1B shows the difference in longitudinal trend between drugs. Eyes on aflibercept achieved larger gains in VA than ranibizumab which are statistically significant from the first week onwards to 12 months.

Macular thickness

Both drugs were effective in reducing macular thickness (Table 2). Mean baseline CST (SD) was very similar (ranibizumab 614 (240) μm versus aflibercept 616 (234) μm; p = 0.95); however, at 12 months, the mean CST (SD) was significantly lower in the aflibercept group at 313 (157) μm versus 370 (180) μm in the ranibizumab group (p = 0.01). The difference in crude effect on CST of aflibercept compared with ranibizumab was more marked in the 121 eyes (41%) presenting with poor VA ≤ 35 letters (Table S1). This subset presented with similar mean CST of 716 (286) μm in the aflibercept group versus 693 (256) μm in the ranibizumab group (p = 0.67); however, the aflibercept-treated eyes had lower final CST of 296 (145) μm versus 388 (218) μm (p = 0.03) and greater crude CST change of −419 (−498, −341) μm versus −305 (−389, −221) μm (p = 0.08), than the ranibizumab-treated eyes at 12 months.

Application of a generalized additive mixed model predicted a greater mean adjusted CST change (95% CI) for aflibercept of −304 (−276, −333) μm vs. −252 (−220, −282) for ranibizumab (p < 0.001). The statistically significant longitudinal trend favouring aflibercept

Table 1. Demographic characteristics of all treatment-naïve CRVO eyes commencing ranibizumab or aflibercept treatment 2014–2019.

	Overall	Ranibizumab	Aflibercept	p-value
Eyes, *n*	296	125	171	
Patients, *n*	291	122	170	
Female, %	47%	47%	47%	1.00
Age, mean (SD)	72 (13)	73 (12)	71 (13)	0.14
VA, mean (SD)	40.1 (25.8)	36.9 (26)	42.5 (25.5)	0.07
≥70 letters, %	13%	13%	13%	1.00
≤35 letters, %	41%	45%	38%	0.29
FFA Performed, *n* (%)*	176 (59%)	75 (60%)	101 (59%)	0.96
Macular Ischaemia, *n* (%)	20 (7%)	9 (7%)	11 (6%)	0.81
Peripheral Ischaemia, *n* (%)	75 (25%)	37 (30%)	38 (22%)	0.16
CST, mean (SD)	615 (236)	614 (240)	616 (234)	0.96
Hypertension, %	60%	58%	61%	0.80
Glaucoma, %	16%	14%	17%	0.53
Country, %				
Australia	29%	30%	29%	
France	31%	39%	25%	
Switzerland	24%	15%	32%	
United Kingdom	15%	16%	15%	

n = number, SD = standard deviation, VA = visual acuity (logMAR letters), FFA = fundus fluorescein angiography, CST = central subfield thickness (in microns).
* Not mandatorily performed or documented.

Table 2. 12-month outcomes in all eyes and stratified by anti-VEGF agent received. Significant p-values comparing ranibizumab and aflibercept are highlighted in bold.

	Overall	Ranibizumab	Aflibercept	p-value
No of Eyes	296	125	171	
Baseline VA, mean (SD)	40.1 (25.8)	36.9 (26)	42.5 (25.5)	0.07
Final VA, mean (SD)	51.9 (28.5)	46.9 (29.4)	55.5 (27.3)	**0.01**
Crude VA change, mean (95% CI)	11.8 (9, 14.5)	9.9 (5.8, 14.1)	13.1 (9.4, 16.8)	0.26
Adjusted VA change, mean (95% CI)†		9.8 (5.5, 14.1)	16.6 (12.9, 20.4)	**0.001**
Gained ≥ 15 letters (%)	46%	40%	50%	0.10
Lost ≥ 15 letters (%)	10%	10%	11%	0.95
VA ≥ 70%Baseline / %Final	13% / 37%	13% / 30%	13% / 42%	1.00/ 0.05
VA ≤ 35%Baseline / %Final	41% / 28%	45% / 34%	38% / 24%	0.29/ 0.09
CST Baseline, mean (SD)	615 (236)	614 (240)	616 (234)	0.95
CST Final, mean (SD)	336 (169)	369 (179)	314 (159)	**0.01**
CST Change, mean (95% CI)	-279 (−311, −247)	-245 (−292, −197)	-302 (−345, −258)	0.10
Adjusted CST Change, mean (95% CI)†		-252 (−220, −282)	-304 (−276, −333)	**<0.001**
Completers, *n* (%)	236 (80%)	99 (79%)	137 (80%)	0.70
Switchers, *n* (%)	35 (12%)	26 (21%)	9 (5%)	**<0.001**
Lost to follow-up, *n* (%)	60 (20%)	26 (21%)	34 (20%)	
Injections, median (Q1, Q3)*	7 (5, 9)	6 (4, 9)	8 (5, 9)	0.62
Visits, median (Q1, Q3)*	10 (8, 13)	10 (7, 13)	10 (8, 13)	0.84

n = number, VA = visual acuity, SD = standard deviation, CI = confidence interval, CST = central subfield thickness, Q1 = first quartile, Q3 = third quartile.
All eyes – includes completers, switchers and non-completers. 'Completers' – eyes with 12 months of observation from the start of treatment, 'switchers' – eyes receiving ≥2 injections of the other treatment drug prior to completion of 12 months from the start of treatment. Observations were included in the analysis only up to the first occurrence of switching agents. 'Non-Completers' – eyes not completing 12 months of observations from the start of treatment.
* Last observation carried forward for switchers and non-completers.
† Calculated from longitudinal models adjusting for age and baseline VA (fixed effects), and practice and intra-patient correlation for bilateral cases (random effects).

is shown in Fig. 1C,D extending from the first 2 weeks through 12 months.

Treatments and visits

The completers (80%) in the aflibercept group had a median (Q1, Q3) of 8 (5, 9) injections, and 10 (8, 13) visits, while the completers (79%) in the ranibizumab group had 6 (4, 9) injections and 10 (7, 14) visits (p = 0.62, 0.84; Table 2). Thus, aflibercept-treated eyes received somewhat more injections, but this difference was not statistically significant. The range in injections delivered was from 1 to 13 over 12 months. Both groups received a similar number of injections: completers had a mean total of 7.4 injections (7.5 aflibercept, 7.2 ranibizumab) over 12 months. The mean number of injections in the first 6 months was 4.8 (4.8 aflibercept, 4.7 ranibizumab), and 2.6 (2.7 aflibercept, 2.6 ranibizumab) in the second 6 months. The median time between each of the 1st to 5th injections was 4, 4, 6 and 6 weeks. Twenty-nine eyes received fewer than 4 injections, and in 12 of these, the final was VA <20 letters; however, in the other 17 eyes, the median final VA was 76 (55, 80) letters at 12 months. Cataract surgery was performed in 9 ranibizumab-treated eyes and 4 aflibercept eyes with YAG capsulotomy performed in one eye from each group.

Inactivity, switching and loss to follow-up

Kaplan–Meier survival analysis was used to compare ranibizumab and aflibercept in terms of time to first grading of inactivity, switching and loss to follow-up (Fig. 2). Inactivity was recorded at least once in 12 months in 227 eyes (96% of completers), with the first occurrence at a median (Q1, Q3) of 58 (29, 98) days. The Cox-proportional hazards model predicted aflibercept achieved inactivity sooner than ranibizumab (p = 0.02).

Thirty-five eyes (12%) switched treatment within 12 months, more commonly from ranibizumab (26 eyes, 21%) than from aflibercept (9 eyes, 5%) (p < 0.001) (Table 2). The median (Q1, Q3) time to switching for all eyes combined was 155 days (112, 252). Eyes switched from ranibizumab to a dexamethasone implant (6 eyes), to aflibercept (17 eyes) or to bevacizumab (2 eyes) with a median VA of 59 (36, 65) letters at the time of switch. Eyes switched from aflibercept with a lower median VA of 45 (29, 50) letters at the time of switch to a dexamethasone implant (5 eyes) or ranibizumab (4 eyes).

Sixty eyes (20%) dropped out before 12 months. The non-completion rate was similar in the ranibizumab group (21%) and the aflibercept group (20%). The overall median (Q1, Q3) time to dropout was 193 days (119, 271). Documented reasons for loss to follow-up included 2 deaths, a medical contraindication in 1 patient, futility of treatment in 3 eyes, 7 patients declined further treatment while 10 patients went to another doctor.

Adverse events

Macular changes affecting vision were newly observed during follow-up in 28 eyes (ERM, macular hole, pigment clumping, atrophy) with a mean (SD) baseline VA of 15 (20) letters and mean 12-month VA of 22 (28) letters. Neovascular complications in either the anterior segment (16 eyes) or posterior segment (17 eyes) led to poor outcomes with a combined mean (SD) VA of 13 (21) letters at 12 months. Eighty-three eyes received panretinal photocoagulation with a 12-month mean VA (SD) of 36 (30) letters from a baseline VA of 26 (28.5) letters. Eyes receiving PRP (83 eyes) had fewer injections (SD) with 6.4 (3.4) compared to 7.3 (3) in eyes that did not receive PRP (p = 0.04). Vitreous haemorrhage was reported in 13 eyes that received a mean (SD) of 3.8 (2.7) injections. Significantly fewer injections 2.5 (1.6) were given to 16 eyes that developed rubeotic glaucoma compared to the rest of the cohort (p < 0.001). Rubeotic glaucoma developed more often in ranibizumab-treated eyes (12 eyes vs 4 aflibercept-treated eyes; p = 0.01); however, these eyes received fewer injections 1.8 injections vs. 4.25 injections respectively.

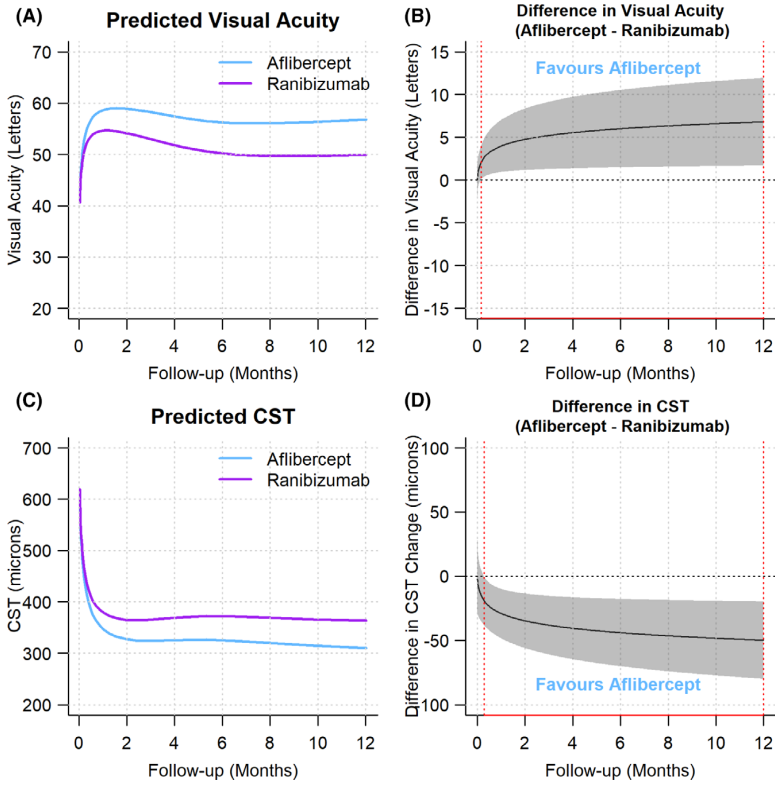

Fig. 1. Graphical representation of vision and CST by drug. Predictions from longitudinal generalized additive models of adjusted visual acuity (A, B) and CST (C, D). Red dotted lines in (B, D) indicate periods in which the confidence interval of the difference between drugs no longer crosses zero.

Injection numbers overall, irrespective of the agent, were strongly associated with rubeotic glaucoma occurrence ($p < 0.001$) suggesting the injection number rather than the drug was associated with rubeotic glaucoma. There was one retinal detachment with VA at 12 months of light perception but no reported cases of endophthalmitis or traumatic cataract following 1915 injections.

Discussion

We report significant improvements in VA and reductions in macular thickness in eyes receiving aflibercept or ranibizumab treatment for CRVO in routine clinical practice. Both groups were well-matched for gender, age, visual acuity and CST at baseline. Both groups had similar numbers of visits and injections during the 12-month period. Our comparative analysis found that eyes receiving aflibercept had greater visual gains and reductions in CST.

Significant differences in the molecular structure and mode of action of the drugs we studied may be the reason for the better outcomes we found with aflibercept for CRVO. While ranibizumab is a humanized monoclonal antibody, aflibercept acts as a decoy-receptor for VEGF and may offer superior VEGF suppression due to higher binding affinity against VEGF (Papadopoulos et al. 2012) as well as longer intravitreal half-life (Stewart & Rosenfeld 2008). This may be particularly important in eyes with CRVO, which have very high vitreous levels of VEGF (Aiello et al. 1994).

While treatment is mandated in RCTs, treatment patterns greatly differ in routine clinical practice due to various factors, including patient compliance, cost and individual re-treatment preferences. As a consequence, the number of injections is often lower than in RCTs as observed in the current analysis and other database studies (Lotery & Regnier 2015). Many analyses of outcomes from routine clinical practice have reported 4–5 injections for CRVO in the first year, in contrast to RCTs which gave on average 8.8–9.6 aflibercept injections (Campochiaro et al. 2011) or 8.4 ranibizumab injections (Brown et al. 2013; Korobelnik et al. 2014) within the first 12 months. Centres participating in the current analysis gave more injections than have previously been reported from routine clinical practice (a median of 7 for both aflibercept and ranibizumab), which is only slightly fewer than in RCTs.

The combination of stronger and potentially longer VEGF suppression of aflibercept may be one of the main drivers for better clinical outcomes since the more prolonged suppression may compensate for the somewhat lower number of injections. Cystoid macula oedema secondary to CRVO may be a particularly attractive indication for new longer acting anti-VEGF agents.

Patient population

The patient population in this analysis from routine clinical practice was older (mean 72 years) than patients included in RCTs using aflibercept or ranibizumab (range 61.5–69.7 years) (Campochiaro et al. 2011; Brown et al. 2013; Korobelnik et al. 2014; Larsen et al. 2018). Patient eyes in the current analysis had worse average baseline VA scores (40.1 letters) than those included in RCTs (range 47.4–53 letters), with less thickened mean baseline CST of 615 µm (range in RCTs 665–693 µm) (Campochiaro et al. 2011; Brown et al. 2013; Korobelnik et al. 2014; Larsen et al. 2018).

Visual outcomes and macular thickness

Visual outcomes for aflibercept and ranibizumab, both adjusted (16.6 and 9.8) and unadjusted (13.1 and 9.9), from this analysis were slightly inferior to those observed in RCTs (13.9 to 18.9 letters; Campochiaro et al. 2011; Brown et al. 2013; Korobelnik et al. 2014; Scott et al. 2017). Lower gains in vision observed in this study were likely due to differences in baseline characteristics and lack of mandated treatment every 4 weeks in the first 6 months. Also, the time from the occurrence of the CRVO to treatment

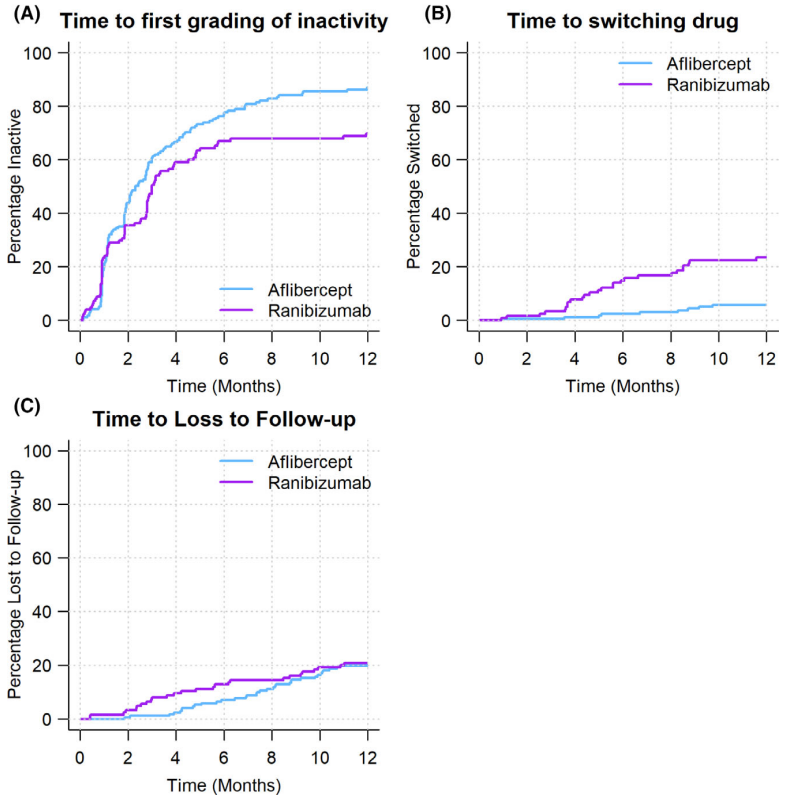

Fig. 2. Kaplan–Meier curve for first grading of inactivity, time to switching and dropout by drug.

initiation was not limited as in RCTs. Fundus fluorescein angiography, performed in around 60% of eyes, was evenly distributed between both treatment groups. A total of 7% and 25% of eyes showed signs of macular ischaemia and peripheral ischaemia respectively. It seems unlikely that eyes with macular ischaemia contributed significantly to the observed reduced VA gains of the total cohort, since previous reports in ranibizumab-treated eyes found that macular ischaemia did not influence VA outcomes (Larsen et al. 2016; Tadayoni et al. 2017).

Aflibercept-treated eyes had more significant reductions in CST than ranibizumab-treated eyes. The Cox-proportional hazards model predicted that aflibercept was significantly faster in achieving CMO inactivity than ranibizumab ($p = 0.02$).

Switching treatments and loss of follow-up

Switching occurred in around 12% of eyes, mainly from ranibizumab (21%) rather than from aflibercept (5%). The reason for switching was not recorded. We hypothesize that it might have included a perceived lack of response by the treating physician. Loss of follow-up was observed in 20% of eyes, which is comparable to other observational studies. Ranibizumab was approved for the treatment of CME secondary to CRVO much earlier than aflibercept. This might have influenced the decision to switch too.

Adverse events

The rate and nature of adverse events, such as macular atrophy, pigment clumping or epiretinal membrane, in our study population was relatively low and about the same as in other diseases treated with intravitreal anti-VEGF such as diabetic retinopathy or age-related macular degeneration.

An important detail is the number of lasers and the fact that, despite anti-VEGF treatment, rubeotic glaucoma developed in 16 eyes – those eyes had significantly fewer injections than the rest of the cohort (mean 2.5 [1.6]). It has now been established that the requirement for panretinal laser photocoagulation in proliferative diabetic retinopathy can be reduced by anti-VEGF therapy (Writing Committee for the Diabetic Retinopathy Clinical Research et al. 2015; Sivaprasad et al. 2017). With the relatively higher VEGF levels in patients with CRVO, one might expect a similar benefit from anti-VEGF therapy (Aiello et al. 1994). However, the evidence base is not as clear for the risk of neovascularization in eyes with CRVO receiving anti-VEGF therapy, especially when treatment is stopped. Data from routine clinical practice may provide useful insights to the development and management of rubeosis in eyes receiving VEGF inhibitors for CRVO.

Strengths and weaknesses

The current analysis has limitations that are inherent to studies using data from routine clinical practice. In contrast to RCTs, treatment decisions are based on the physician's observation in consultation with the patient. The choice of when to treat and to schedule the next appointment also relies on the patient's availability to integrate frequent appointments into a busy work scheduled. Normally, no reading centre recommendations or protocols are followed as is the case in RCTs. There was no randomization to treatment groups, which, while not significant, resulted in some differences in baseline characteristics. We accounted for this partially by adjusting for baseline factors that might impact the outcome, such as age, VA and CST.

The strengths of the current study are the large sample size and an adequate representation of how anti-VEGF drugs are used in routine clinical practice in a number of centres that treat CRVO. The present study, which had fortuitously well-matched baseline characteristics, is unlikely to overestimate either of the drugs' effectiveness (Concato et al. 2000).

Observational studies may suffer from poor data quality. For example, baseline and 12-month visual acuity values could only be identified in around half of the 30 000 otherwise eligible eyes with neovascular age-related macular degeneration in a recent analysis from the IRIS database

(Kiss et al. 2020). By contrast, the FRB! database only accepts 'finalized' data which is 100% complete and within prespecified ranges, the finalization rate is consistently above 95%.

Conclusions

This study found that both aflibercept and ranibizumab improved VA and reduced macular thickness over 12 months in eyes with CRVO. Aflibercept led to significantly greater improvements, both in VA and CST. Longer-term observational studies are warranted to verify whether the initial benefit of aflibercept and ranibizumab is maintained.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. 12 Month outcomes in CRVO eyes with Baseline VA ≤35 Letters and VA >35 Letters and stratified by Anti-VEGF agent received.

Twelve-month outcomes of ranibizumab versus aflibercept for macular oedema in branch retinal vein occlusion: data from the FRB! registry

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ABSTRACT

Background/Aims To compare the efficacy of ranibizumab (0.5 mg) with aflibercept (2 mg) in the treatment of cystoid macular oedema due to branch retinal vein occlusion (BRVO) over 12 months.

Methods A multicentre, international, database observational study recruited 322 eyes initiating therapy in real-world practice over 5 years. The main outcome measure was mean change in EDTRS letter scores of visual acuity (VA). Secondary outcomes included anatomic outcomes, percentage of eyes with VA >6/12 (70 letters), number of injections and visits, time to first inactivity, switching or non-completion.

Results Generalised mixed effect models demonstrated that mean (95% CI) adjusted 12-month VA changes for ranibizumab and aflibercept were similar (+10.8 (8.2 to 13.4) vs +10.9 (8.3 to 13.5) letters, respectively, p=0.59). The mean adjusted change in central subfield thickness (CST) was greater for aflibercept than ranibizumab (−170 (−153 to −187) µm vs −147 (−130 to −164) µm, respectively, p=0.001). The overall median (Q1, Q3) of 7 (4, 8) injections and 9 (7, 11) visits was similar between treatment groups. First grading of inactivity occurred sooner with aflibercept (p=0.01). Switching was more common from ranibizumab (37 eyes, 23%) than from aflibercept (17 eyes, 11%; p=0.002).

Conclusion Visual outcomes at 12 months in this direct comparison of ranibizumab and aflibercept for BRVO in real-world practice were generally good and similar for the 2 drugs, despite a greater effect of aflibercept on CST and time to first grading of inactivity.

INTRODUCTION

Randomised controlled trials (RCTs) have provided the safety and efficacy data for ranibizumab and aflibercept to become first-line treatments recommended in international guidelines for cystoid macular oedema (CMO) secondary to branch retinal vein occlusion (BRVO).[1–7] Less is known about the outcomes in real-world clinical practice. Evidence from routine care can complement RCTs since they have higher levels of external validity that is more generalisable to the broader population.[8]

Current evidence derived from routine care regarding vascular endothelial growth factor (VEGF) inhibitors for BRVO includes a heterogeneous series of retrospective reviews, mainly in single centres, studying various treatment regimens, often in combination with, or compared with, laser or steroids. Most studies concern ranibizumab and bevacizumab.[9–21] A systematic review of real-world BRVO studies concluded that the visual and anatomic improvements were less impressive than in RCTs, with fewer injections in the real-world studies.[22]

The UK EMR Users Group recently reported outcomes of treatment with either anti-VEGF, steroids or laser in 5661 patients with BRVO, with 80% loss to follow-up at 12 months.[23] The LUMINOUS study enrolled 326 eyes with treatment-naïve BRVO receiving ranibizumab with 54% loss to follow-up at 12 months.[24]

The Fight Retinal Blindness! outcomes registry has provided data on real-world outcomes for neovascular age-related macular degeneration,[25–27] and for diabetic macular oedema treated with VEGF inhibitors.[28] The aims of this study were to report real-world outcomes and comparative analysis of ranibizumab and aflibercept, in treatment-naïve eyes with CMO due to BRVO using observational data tracked in a large international patient registry.

MATERIALS AND METHODS

Design and setting

This was an international, multicentre, retrospective study using data from the retinal vein occlusion module of the web-based Fight Retinal Blindness! registry.[29] The study followed the Strengthening the Reporting of Observational Studies in Epidemiology checklists for reporting observational studies.[30]

Data sources and measurements

Treatment decisions and timing were at the discretion of the physician and patient, reflecting routine clinical practice. Mandatory data points were populated at each clinical visit via a web-based interface. Variables were either numeric, mutually exclusive or a selection from a drop-down menu. Logarithm of the minimum angle of resolution (logMAR) visual acuity (VA) (best of uncorrected, corrected or pinhole) was expressed in letters read . Macular

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oedema, including central subfield thickness (CST in µm), was assessed with optical coherence tomography using the same machine for the same patient throughout. The presence of CMO (active or inactive) was judged by the practitioner. Other observations recorded at each visit included any treatments given, other procedures performed and adverse events. Enrolment in the audit required a baseline visit when the first injection was administered that had extra data points regarding demographics, the type of RVO, presence or absence of key risk factors and ischaemia if fluorescein angiography was performed.

Patient selection

We studied treatment-naïve patients with CMO due to BRVO that commenced treatment with either aflibercept (2 mg Eylea, Bayer) or ranibizumab (0.5 mg Lucentis, Genentech/Novartis) between 1 June 2014 and 1 June 2019. Central and hemi-retinal vein occlusions were excluded. Eligible patients must have had at least three visits to establish sufficient ongoing follow-up. 'Completers' were defined as having ≥12 months of follow-up. We defined 'switchers' as eyes that received at least two injections of an alternative agent.

Outcomes

The primary outcome measure was mean change from baseline VA at 12 months. Secondary outcomes included mean change in CST, visits, injections and the proportion of eyes with VA >6/12 (70 letters). Event-based outcomes included time to first grading of inactivity, switching drugs and non-completion over 12 months. Outcomes were studied overall and comparatively between ranibizumab and aflibercept.

Statistical analysis

Baseline and demographic characteristics were summarised with descriptive statistics, including counts and percentages for categorical variables; and mean, SD, median, first and third quartiles (Q1, Q3) for continuous variables. Observations began at the first treatment visit and continued until the 12-month visit (365±30 days). We compared baseline characteristics of the ranibizumab and aflibercept groups with t-tests, Wilcoxon signed-rank 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 and switchers. The last observation in switchers was when the first treatment with the alternative agent was delivered.

Generalised additive mixed effects models were used to compare longitudinal changes in VA and CST with the interaction between treatment and time as the main predictor. We included adjustments for age and baseline VA or CST as fixed effects, while nesting of outcomes within doctor and patient (bilateral cases) were included as random effects. The longitudinal models included all eyes but did not include visits after the first alternative agent was delivered in switchers. The longitudinal models were plotted and analysed to compare adjusted VA and CST outcomes for each drug.

Number of injections and visits were calculated for completers and compared by group in all eyes up to completion, non-completion or switching with generalised Poisson mixed models with an offset for log days of follow-up. Kaplan-Meier survival curves were generated for time to switching, non-completion and first physician grading of CMO inactivity. The time to inactivity for each agent was compared with a Cox-proportional hazards model. Age, baseline VA and baseline CST were considered fixed effects, while random effects addressed nesting under each physician's care or within a single patient (bilateral cases).

Analysis was performed in R V.4.0.0 (cran.r-project.org) using the *glmmTMB* (V.1.0.1) and *mgcv* (V.1.8-31) packages for generalised linear and generalised additive mixed models, respectively.[31] The *survival* (V.3.1-12) package was used to generate the Kaplan-Meier estimates, and *coxme* (V.2.2-16) for Cox mixed effects models.[31]

Table 1 Baseline characteristics of all treatment-naïve BRVO eyes commencing treatment with ranibizumab or aflibercept

	Overall	Ranibizumab	Aflibercept	P value
Eyes, n	322	162	160	
Patients, n	319	162	157	
Female, % patients	54%	50%	57%	0.22
Age, mean (SD)	70 (12)	70 (13)	71 (11)	0.44
VA, mean (SD)	55.6 (19.1)	54.3 (19.4)	56.9 (18.7)	0.21
≥70 letters (6/12), %	30%	28%	32%	0.58
≤35 letters (6/60), %	16%	17%	14%	0.68
FFA performed, n (%)*	151 (47%)	84 (52%)	67 (42%)	0.09
Macular ischaemia, n (%)	16 (5%)	10 (6%)	6 (4%)	0.75
Peripheral ischaemia, n (%)	49 (15%)	30 (19%)	19 (12%)	0.43
CST, mean (SD)	466 (156)	475 (164)	456 (148)	0.30
Hypertension, %	68%	70%	66%	0.35
Glaucoma, %	8%	7%	8%	0.97
Country, %				
Australia	36%	33%	39%	
France	13%	15%	11%	
Ireland	9%	9%	9%	
UK	20%	18%	22%	
Spain	21%	25%	18%	

*Not mandatorily performed or documented.
BRVO, branch retinal vein occlusion; CST, central subfield thickness (in µm); FFA, fundus fluorescein angiography; n, number; VA, visual acuity (logMAR letters).

RESULTS

Study participants

We identified 322 treatment-naïve eyes with CMO due to BRVO that started treatment with ranibizumab (162 eyes) or aflibercept (160 eyes) between 1 June 2014 and 1 June 2019 (table 1).

Baseline demographic characteristics were broadly similar between the two treatment groups. The mean baseline VA (SD) was around 6/24 and was slightly higher in the aflibercept group, but this was not significant (ranibizumab 54.3 (19.4) letters vs aflibercept 56.9 (18.7); p=0.21). The mean baseline CSTs (SD) were also similar (ranibizumab 475 µm (164) vs aflibercept 456 µm (148); p=0.30).

Visual outcomes

The crude, unadjusted mean 12-month VA change (95% CI) was +13.0 (10.1 to 15.9) letters for ranibizumab versus +10.9 (8.4 to 13.4) for aflibercept (p=0.80) (table 2).

Around 40% of eyes gained ≥15 letters (ranibizumab 41% vs aflibercept 40% (p=0.98)) and 60% of eyes had 12-month VA >6/12 (ranibizumab 59% vs aflibercept 61% (p=0.80)) compared with 30% at baseline (ranibizumab 28% vs aflibercept 32% (p=0.58)). Fourteen eyes (4%, 7 eyes from each group) lost ≥15 letters with mean VA decreasing from 58 letters at baseline to 35 letters (6/60) at 12 months. Eighteen eyes had a final VA ≤6/60 after 12 months (ranibizumab 8 (6%) vs aflibercept 10 eyes (7%); p=0.80), but these eyes started with a mean baseline

Table 2 12-Month outcomes in BRVO eyes—overall and stratified by anti-VEGF agent received

	Overall	Ranibizumab	Aflibercept	P value
Eyes, n	322	162	160	
Baseline VA, mean (SD)	55.6 (19.1)	54.3 (19.4)	56.9 (18.7)	0.21
Final VA, mean (SD)	67.6 (17.9)	67.3 (18)	67.8 (17.8)	0.80
Crude VA change, mean (95% CI)	12.0 (10 to 13.9)	13.0 (10.1 to 15.9)	10.9 (8.4 to 13.4)	0.28
Adjusted VA change, mean (95% CI)*		10.8 (8.2 to 13.4)	10.9 (8.3 to 13.5)	0.59
Gained ≥15 letters (%)	40%	41%	40%	0.98
Lost ≥15 letters (%)	4%	4%	4%	1.00
VA≥70 %Baseline/%Final	30/60	28/59	32/61	0.58/0.80
VA≤35 %Baseline/%Final	16/6	17/6	14/7	0.68/0.80
CST baseline, mean (SD)	466 (156)	475 (164)	456 (148)	0.30
CST final, mean (SD)	310 (104)	317 (109)	303 (98)	0.23
CST change, mean (95% CI)	−155 (−173 to −137)	−158 (−182 to −133)	−153 (−180 to −127)	0.81
Adjusted CST change, mean (95% CI)*		−147 (−130 to −164)	−170 (−153 to −187)	**0.001**
Completers, n (%)	259 (80)	130 (80)	129 (81)	0.93
Switchers, n (%)	54 (17)	37 (23)	17 (11)	**0.002**
Lost to follow-up, n (%)	63 (20)	32 (20)	31 (19)	
Injections, median (Q1, Q3)†	7 (4, 8)	6 (4, 9)	7 (4, 8)	0.75
Visits, median (Q1, Q3)†	9 (7, 11)	9 (7, 11)	9 (8, 12)	0.80

All eyes—includes completers, switchers and non-completers. 'Completers'—eyes with 12 months of observation from the start of treatment, 'switchers'—eyes receiving ≥2 injections of the other treatment drug prior to completion of 12 months from the start of treatment. Observations were included in the analysis only up to the first occurrence of switching agents. "Non-completers'—eyes not completing 12 months of observations from the start of treatment.
Significant P values comparing ranibizumab and aflibercept are highlighted in bold.
*Calculated from longitudinal models adjusting for age and baseline VA (fixed effects), and practice and intrapatient correlation for bilateral cases (random effects).
†Last observation carried forward for switchers and non-completers.
BRVO, branch retinal vein occlusion; CST, central subfield thickness; n, number; Q1, first quartile; Q3, third quartile; VA, visual acuity.

VA of 6/60. Individual eyes that had poor outcomes are discussed in '*Adverse events*'.

The mean VA change (95% CI) adjusted using the generalised additive mixed model described in '*Materials and methods*' was +10.8 (8.2 to 13.4) letters in the ranibizumab group versus +10.9 (8.3 to 13.5) for aflibercept (p=0.59). The mean adjusted VA over 12 months for each group is shown in figure 1A. Adjusted mean VA change peaked at around 8 months (+13.1 (10.9 to 15.3) letters for ranibizumab, +13.2 (10.9 to 15.4) for aflibercept) with some erosion of those gains out to 12 months. Subtracting the ranibizumab model from the aflibercept model, figure 1B shows similar predicted mean VA changes between the two treatment groups over 12 months.

Macular thickness

Both drugs were effective in reducing macular thickness (table 2). Mean unadjusted final CST (SD) was slightly lower in the aflibercept group at 303 (98) μm vs 317 (109) μm in the ranibizumab group (p=0.23). The unadjusted change in CST was similar between drugs but after adjusting for baseline CST and age, the mean adjusted CST change (95% CI) was significantly greater for eyes in the aflibercept group at −170 (−153 to −187) μm vs −147 (−130 to −164) μm in the ranibizumab group (p=0.001). The statistically significant longitudinal trend favouring aflibercept is shown in figure 1C,D.

Treatments and visits

Completers (80%) had a median (Q1, Q3) of 7 (4, 9) injections over a median (Q1, Q3) of 9 (7, 11) visits without any significant difference between agents (p=0.75 and p=0.80, respectively) (table 2). The median intervals between the first to fifth injections were 28, 28, 42 and 42 days in both groups. The mean number of injections given between 6 and 12 months was 1.9 (2.0 on aflibercept, 1.9 on ranibizumab). Sixty-nine eyes with complete follow-up (27%) had a median final VA of 6/9.5 after receiving ≤3 injections over 12 months, as did 78 eyes (31% of completers) that had no injections in the final 6 months. Macular laser was applied to seven eyes (2%) during the 12 months at a median of 105 days; to four eyes in the ranibizumab group, and three eyes in the aflibercept group.

Inactivity, switching and loss to follow-up

Time to first grading of inactivity, switching and loss to follow-up were analysed with Kaplan-Meier estimates to compare agents (figure 2). A first grading of inactivity with aflibercept was more likely to occur over time than with ranibizumab after adjustment with the Cox-proportional hazards model (p=0.01). The median (Q1, Q3) time to inactivity for eyes receiving aflibercept was 84 (56, 100) days vs 88 (41, 159) days for ranibizumab.

Fifty-four eyes (17%) switched treatment within 12 months (table 2). Switching was more common in the ranibizumab group (37 eyes, 23%) than in the aflibercept group (17 eyes, 11%; p=0.002). Thirty-two eyes from the ranibizumab group eyes switched to aflibercept and five switched to a dexamethasone implant. Seven aflibercept eyes switched to ranibizumab, two to bevacizumab and six to a dexamethasone implant. Overall switching within the first 12 months occurred after a median (Q1, Q3) of 172 (111, 285) days. The median (Q1, Q3) VA at the time of switching was around 6/15, with 65 (50, 70) letters in the ranibizumab group and 68 (58, 75) letters in the aflibercept group. The 11 eyes overall that switched to dexamethasone also had VA around 6/15 or 65 (55, 73) letters when they switched at a median of 280 (151, 332) days.

Sixty-three eyes (20%) did not complete 12 months of follow-up, with similar rates in the ranibizumab (20%) and aflibercept group (19%). The overall median (Q1, Q3) time to dropout was 217 days (156, 266) with a median VA (Q1, Q3) before dropout of 72 (58, 81) letters (approximately 6/12 (6/19,

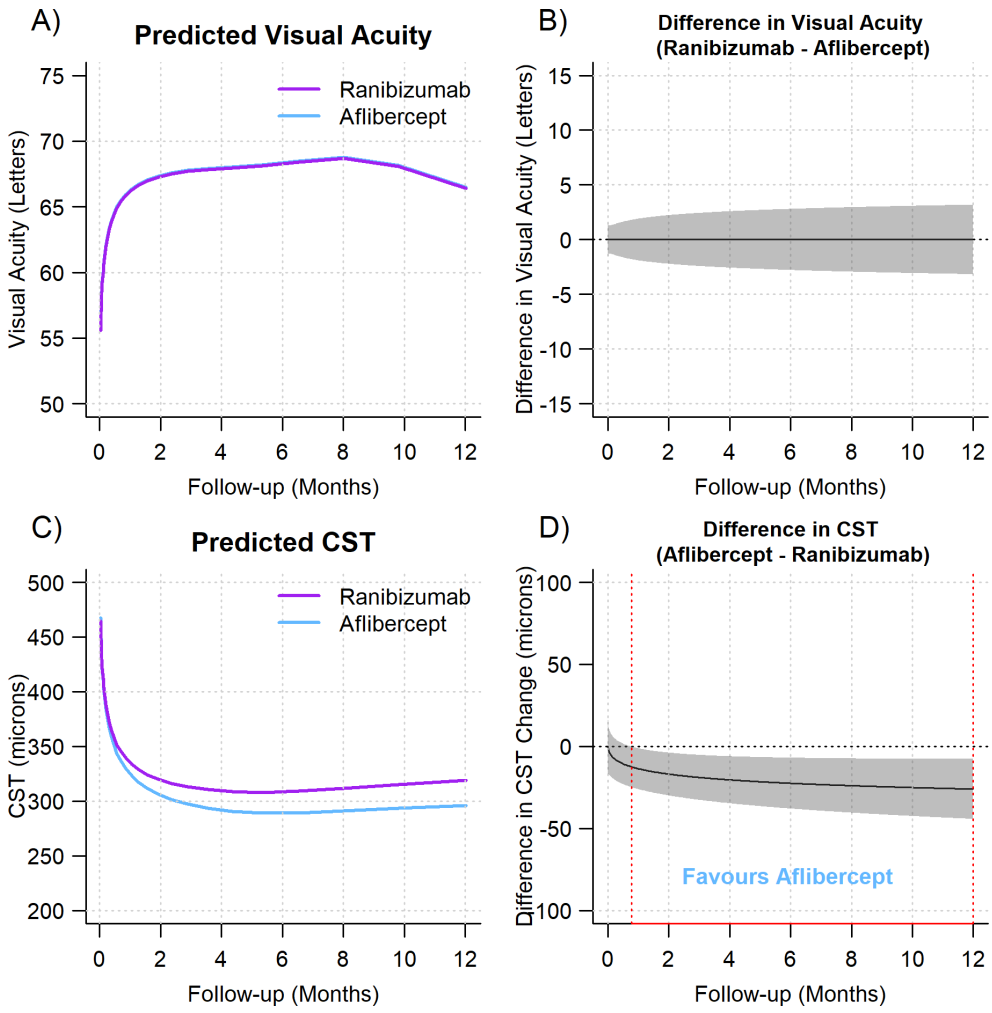

Figure 1 Predictions from longitudinal generalised additive models of adjusted visual acuity (A and B) and central subfield thickness (CST) (C and D) by drug. Red dotted lines in (D) indicate periods in which the CI of the difference between drugs no longer crosses zero.

6/7.5)). Documented reasons for loss to follow-up included three deaths, six patients declined further treatment, further treatment was considered futile in one eye, while seven patients went to another doctor.

Adverse events

Macular changes affecting vision occurred during the study in 24 eyes (epiretinal membrane, macular hole, pigment clumping, atrophy). The median VA (Q1, Q3) at 12 months in this group was around 6/19 or 60 (44, 69) letters but did include three of the eyes that lost ≥15 letters and four eyes that had a final VA of ≤6/60. Posterior segment neovascularisation was reported in 1 eye, but 35 eyes (21 ranibizumab, 14 aflibercept; p=0.3) received sector photocoagulation at a median (Q1, Q3) of 106 (49, 225) days. These eyes still received a median of 8 (5, 9) injections over 12 months and were confined to five centres (18%). Vitreous haemorrhage occurred in two eyes. There was one reported case of infectious endophthalmitis with a final VA of count fingers, but no traumatic cataract or retinal detachment with a total of 1979 injections.

DISCUSSION

This analysis of treatment outcomes using data from an observational database found that aflibercept and ranibizumab were both effective at improving VA and reducing macular thickness in patients with BRVO 12 months after initiation of treatment. The mean unadjusted and adjusted VA changes were +13.0 and +10.8 letters, respectively, for ranibizumab and were both +10.9 letters for aflibercept (p=0.17, 0.86). Aflibercept was significantly more effective at reducing macular thickness than ranibizumab. The mean final CSTs for aflibercept and ranibizumab were 303 µm vs 317 µm and the adjusted CST changes were −170 µm vs −147 µm, respectively (p=0.23, 0.001). Both groups had a median of seven injections over a similar number of visits. Extension of the interval to 6 weeks after 3 monthly injections was apparent. On average, only two injections were given per eye in the final 6 months. Posterior segment neovascularisation may have been under-reported (one eye). Laser was possibly used to treat retinal ischaemia without neovascularisation in 35 eyes confined to a few centres but without a reduced number of injections.

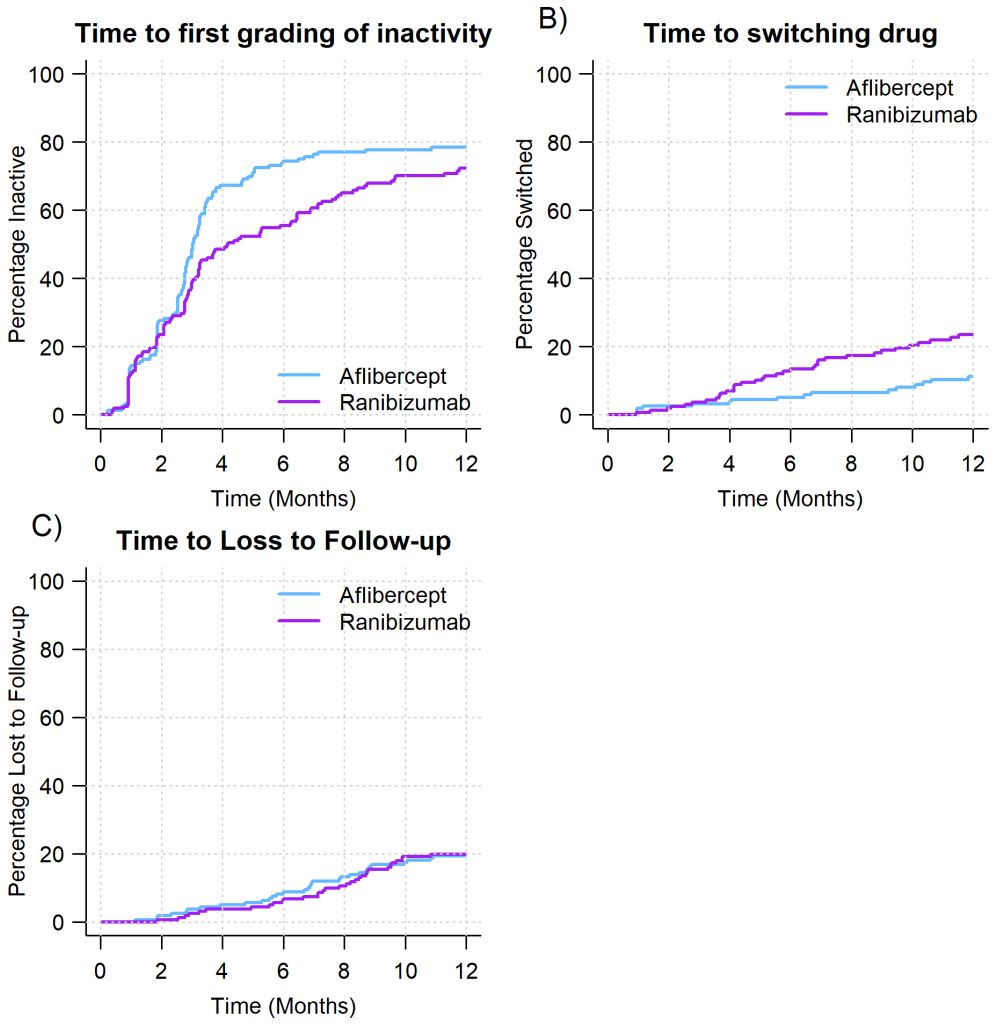

Figure 2 Kaplan-Meier curve for (A) first grading of inactivity, (B) time to switching and (C) dropout by initial injection.

Ranibizumab (0.5 mg) given monthly in the first 6 months in the BRAVO study led to a mean improvement in VA of +18.3 letters and a reduction of CST of −345 μm.[1] Similar changes were reported for monthly aflibercept in the VIBRANT study (+17 letters and −280 μm).[4] Vision gains were maintained at 12 months with flexible or bimonthly treatment, essentially totalling 8.8 and 9.0 injections in the first year of treatment.[2 3] The 2-year BRIGHTER study reported 16 letter gains in VA with a flexible ranibizumab regime after 3 dose loading.[32] An ongoing need for VEGF suppression in many eyes with BRVO beyond 6 months was demonstrated in BRAVO, VIBRANT. In the present study, a mean of 1.9 injections given in the second 6 months may account for the erosion of the peak visual gains seen at 8 months.

The mean baseline CST was low in our study (465 μm) compared with BRAVO (551 μm), BRIGHTER (530–550 μm) and VIBRANT (559 μm) possibly leaving less room for improvement. The baseline vision in our cohort (56 letters), was better than BRAVO (53 letters) but worse than in VIBRANT (58 letters) and BRIGHTER (60 letters). The proportion of eyes achieving 12-month VA>6/12 (70 letters) in the present study was 60% compared with 65% in BRAVO and 85% in VIBRANT.

Under-treatment is typically blamed for less impressive outcomes in the real-world setting.[33] A systematic review of real-world BRVO outcomes analysed 13 ranibizumab treatment arms in various case series and comparative studies involving anti-VEGF, laser or steroids.[9–22] From a baseline of 54 letters and CST of 501 μm, the authors estimated a weighted mean VA change of +15.9 letters, mean CST change of −189.8 μm and a mean of 4.9 ranibizumab injections at 12 months. The studies selected for the meta-analysis still had some artifice placing them somewhere between the real-world and RCTs, for example, many excluded patients with common co-existent retinal pathology,[10 12 13 15–17 19–21] a media opacity or a history of intraocular surgery,[9 10 12 15 17 20] limits were placed on duration of disease[10 12–16 19–21] and they typically followed a protocol which demanded comprehensive investigations at specific time points.[10 12 13 15 17 19–21]

Real-world evidence in its purest form should be derived in a setting indistinguishable from normal practice. Previous studies using extracted data from medical records or from a registry have suffered from poor follow-up. The UK EMR Users Group reported vision gains of +9.6 letters with 5.1 injections in the

26% of 3939 eyes with follow-up at 12 months.[23] The LUMINOUS BRVO study reported +11.9 letter gains with 5.0 injections but also suffered from relatively high loss to follow-up (>50%).[24] In our study, the relatively good VA, at last observation in eyes (20%) that did drop out, of 72 (58, 81) letters suggests that some may have been successfully treated.

There are some limitations in this study in keeping with its observational design. We did not track time from first symptoms, however the mean VA at the time of the first injection was similar to BRAVO and VIBRANT, suggesting there were no untoward delays in starting treatment. The reason for the choice of one drug over the other is not known in each case, although the drug groups had similar baseline characteristics despite lack of randomisation. Regardless, we adjusted for baseline VA, age, CST and nesting within practices in our statistical models. Censoring observations after switching may selectively bias results by removing eyes doing poorly, however, the median VA of the eyes that switched at 65 letters (6/15) was not consistent with this. Eyes that switched to a steroid may have done so for the extended duration rather than a poor visual outcome.

Treatment-naïve BRVO eyes receiving VEGF inhibitors in the routine clinical practice have good outcomes—but still lag behind those of the RCTs. Ranibizumab and aflibercept produced equivalent improvements in VA, despite a greater effect on macular thickness and lesser time to first grading of inactivity afforded by aflibercept. The findings are in keeping with similar observational studies that have demonstrated equivalent efficacy of aflibercept and ranibizumab for neovascular age-related macular degeneration,[25–27] and also concur with the greater reductions in CST from aflibercept over ranibizumab in diabetic macular oedema.[28] An ongoing need for VEGF suppression from 6 to 12 months was evident. VA gains eroded in the last 6 months when only 1.9 injections were given. Further studies are required to investigate the long-term outcomes of BRVO treatment in routine clinical practice beyond 12 months.

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Contributors MG and DB are inventors of the software used to collect the data for this analysis, initiated the collaborative project and revised the paper. HM implemented the trial in the UK designed and revised the paper. VN monitored data collection for the whole trial. ARH implemented the trial in Australia and with VN drafted and revised the statistical analysis plan, cleaned and analysed the data and ARH drafted and revised the paper. ARH is guarantor. CPC-G and MG implemented the trial in France and revised the paper. P-HG and SF-B revised the paper. SA, RPCM and JZ-V implemented the trial in Spain and revised the paper. JA and ILMcA revised the paper. LO'T implemented the trial in Ireland and revised the paper.

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Competing interests MCG and DB are inventors of the software used to collect the data for this analysis. JA, ILMcA and MCG are members of advisory boards for Novartis and Bayer. JA and MCG are also members of advisory boards for Allergan. MCG and JA report personal fees and others from Novartis, others from Bayer, outside the submitted work. DB received a research grant from Novartis.

Patient consent for publication Not required.

Ethics approval Local ethics and data protection approval was obtained from the Royal Australian NZ College of Ophthalmologists and the University of Sydney Human Research Ethics Committees (HREC#16.09), the Caldicott Guardian (Dr Kilian Hynes) of the Royal Free London NHS Foundation Trust (valid until 3 September 2024), Institutional Review Boards of the Mater Private Hospital (IRB, 1/378/2130) in Dublin, Ireland; the Hospital Clinic of Barcelona, Spain (2015/57-OFT-HUSC) and the Société Française d'Ophtalmologie (2017_CLER-IRB_ll-05) in Paris, France. The study adhered to the tenets of the Declaration of Helsinki. All patients gave their informed consent. This consisted of opt-in consent from patients in France, Ireland, Spain and the UK, while the ethics committee in Australia approved the use of opt-out patient consent.

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ORIGINAL ARTICLE – CLINICAL SCIENCE

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One-year real-world outcomes of bevacizumab for the treatment of macular oedema secondary to retinal vein occlusion

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Abstract

Background: Bevacizumab is the only agent that many people can afford, yet there are only limited data on whether it improves macular oedema (MO) secondary to retinal vein occlusion (RVO) in real-world clinical practice. Here we studied 12-month real-world treatment outcomes of bevacizumab for RVO-related MO.

Methods: This was a multicentre, observational study analysing 12-month data from the Fight Retinal Blindness! (FRB) database. We studied treatment-naïve eyes with MO secondary to RVO commencing bevacizumab therapy between June 2009 and June 2019. Visual acuity (VA) and central subfield thickness (CST) were measured at baseline, 6 and 12 months. The primary outcome was a change in VA from baseline to 12 months.

Results: Two hundred and twenty treatment naive eyes were analyzed. The baseline VA for BRVO was better than CRVO (55.8 vs. 42.6 LogMAR letters) and this gap widened over the 12-month period, with a 12-month VA change of +14.0 (95% CI 11.1, 16.8) letters for BRVO and + 11.9 (95% CI 6.4, 17.4) for CRVO. The mean CST at baseline was 511 μm for BRVO and 627 μm for CRVO, falling at 12 months by −155 μm (−190, −121) in BRVO and −198 μm (−252, −145) in CRVO. The median number of injections for BRVO and CRVO completers was 7 (5, 9).

Conclusions: Bevacizumab can be an effective treatment of RVO-MO in a real-world setting with outcomes approaching those reported by the seminal clinical trials. The functional and anatomical outcomes of intravitreal therapy were better for BRVO than CRVO.

KEYWORDS
bevacizumab, cystoid macular oedema, medical retina, retinal vein occlusion

1 | INTRODUCTION

Bevacizumab is the only anti-VEGF agent that is on the WHO's list of essential medicines,[1] and whilst there is a growing body of real-world evidence supporting its use in neovascular macular degeneration and diabetic maculopathy,[2,3] there is a paucity of data on its effectiveness in retinal vein occlusion (RVO).

Randomised controlled trials (RCTs) have established VEGF inhibitors as first-line treatment of macular oedema (MO) associated with branch and central RVO, improving and maintaining visual acuity (VA), whilst reducing central subfield thickness (CST).[4,5] Whilst limited clinical studies suggest that bevacizumab may be as efficacious as ranibizumab and aflibercept,[6,7] there remains a pressing need to evaluate the effectiveness of bevacizumab at treating MO associated with RVO in real-world practice.

The Fight Retinal Blindness! (FRB!) Registry is an international collaboration collecting real-world data on patients with a range of retinal diseases and it has been used by clinicians in both Australia and New Zealand for the past decade. Bevacizumab remains the first-line treatment for RVO-associated MO in New Zealand and was first-line in Australia until late 2016[8] and thus data from Australasia providers using FRB! provide a unique opportunity to evaluate the effectiveness of bevacizumab in the management of RVO. In this study data from FRB! were analysed with the aim of reporting the VA and anatomic outcomes and the frequency of bevacizumab injections over the first year of treatment in eyes with RVO in a real-world setting.

2 | METHODS

2.1 | Design and setting

Multicentre, observational cohort study examining 12-month routine clinical outcomes in treatment naïve patients with RVO receiving bevacizumab within Australia and New Zealand using data from the FRB! Registry.[2] Treatment decisions were the responsibility of the physician reflecting routine clinical care. FRB! registry has a baseline enrolment visit which establishes the type of RVO (Branch, Hemi or Central RVO) and records data from each clinical visit, including the logarithm of the minimum angle of resolution (LogMAR) VA in letters (best of uncorrected, corrected and pinhole), the presence of MO, CST (μm), treatments given, procedures performed, and adverse events. The Royal Australian and New Zealand College of Ophthalmologists and the University of Sydney Human Research Ethics Committees granted ethics approval including the use of opt-out patient consent. The research followed the STROBE guidelines for the reporting of observational studies and adhered to the tenets of the Declaration of Helsinki.[9]

2.2 | Patient selection

The analysis was limited to treatment-naïve patients with RVO that commenced treatment for MO with intravitreal bevacizumab of 1.25 mg (0.05 ml) between 1 June 2009 and 1 June 2019. Patients must have had three or more visits and at least two injections to be included. Eyes with ≥12 months of follow-up were defined as 'Completers'. 'Switchers' were defined as eyes receiving at least two injections of an alternative agent within 12-months. Eyes with CRVO or BRVO were included in this analysis. Eyes with Hemi-RVO were excluded. Exclusion criteria include prior vitrectomy, prior laser treatment, prior anti-VEGF or intravitreal steroid treatment.

2.3 | Outcomes

The primary outcome was mean change in VA from baseline to 12-months. Secondary outcomes included mean change in CST, number of visits and injections, the proportion of eyes with VA > 70 letters. CRVO patients were subdivided by baseline VA, which was used as surrogate marker for ischaemic versus non-ischaemic CRVO as angiographic data were not available for most patients. Time to event analysis over 12 months included first grading of inactivity, switching and non-completion. The grading of lesion activity was performed at all full assessment visits by the attending Clinician. 'Inactivity' was defined by the absence of subretinal and intraretinal fluid. Outcomes were studied for BRVO and CRVO and included sub-groups with baseline VA ≤20 letters and VA > 20 letters with CRVO.

2.4 | Statistical analysis

Descriptive statistics included the mean, standard deviation (*SD*), median, and first and third quartiles (Q1, Q3) for continuous variables and counts and percentages for categorical variables. The baseline visit was defined by the receipt of the first treatment. Observations continued until the final visit closest to 12-months (365 ± 30 days). Last observation carried forward (LOCF) was used for non-completers and switchers to calculate crude visual and anatomic outcomes. In switchers, this was the visit at which the alternative agent was first administered.

TABLE 1 Demographic characteristics of all eyes, BRVO, CRVO including CRVO split into subgroups with baseline VA ≤20 and VA > 20 letters

	All eyes	BRVO	CRVO	CRVO ≤20 letters	CRVO >20 letters
Eyes, *n*	220	135	85	22	63
Patients, *n*	218	133	85	22	63
Female, %	44%	51%	33%	41%	30%
Age, mean year (*SD*)	71 (11.7)	72 (11.1)	70 (12.5)	72 (15.1)	69 (11.5)
VA, mean (*SD*)	50.7 (22.8)	55.8 (18.6)	42.6 (26.4)	4 (3.9)	56 (14.9)
VA > 70 letters, %	21%	22%	20%	0%	27%
VA ≤ 35 letters, %	23%	14%	37%	100%	14%
FFA performed *n* (%)[a]	57 (26%)	37 (27%)	20 (24%)	3 (14%)	17 (27%)
Macular isch. *n* (%)	12 (6%)	10 (7%)	2 (2%)	1 (5%)	1 (2%)
Peripheral isch. *n* (%)	17 (8%)	13 (10%)	4 (5%)	2 (9%)	2 (3%)
CST, mean (*SD*)	556 (211)	511 (187)	627 (227)	722 (311)	595 (183)
Hypertension, %	69%	74%	60%	55%	62%
Glaucoma, %	8%	7%	9%	9%	10%
Country, %					
New Zealand	53%	53%	53%	50%	54%
Australia	47%	47%	47%	50%	46%

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CST, central subfield thickness (in microns); FFA, fundus fluorescein angiography; Isch, ischaemia; *n*, number; *SD*, standard deviation; VA, visual acuity in LogMAR letters.
[a]Not mandatorily performed or documented.

Longitudinal changes in VA and CST were visualised using generalised additive mixed effect models and included all visits up until either completion, non-completion or the first occurrence of alternative intravitreal agent administered in switchers without imputation of missing data. Analysis was performed in R version 4.0.0 and RStudio version 1.2.5042 utilising the *glmmTMB* (1.0.2.1) and *mgcv* (V1.8–33) packages for generalised linear and generalised additive mixed models, respectively.[10–12] The *survival* (3.2–7) package was used to generate the Kaplan Meier estimates.[13]

3 | RESULTS

3.1 | Study participants

There were 220 treatment naïve eyes that started treatment with bevacizumab for MO due to BRVO (135 eyes) or CRVO (85 eyes, 22 with VA ≤20 letters and 63 eyes with VA > 20 letters) between June 2009 and June 2019 (Table 1). Patients with HRVO, $n = 17$, were excluded from the analysis subset due to growing evidence that they behave differently from both CRVOs and BRVOs.[14] The median/mean baseline VA (*SD*) were 60/55.8 (18.6) letters in BRVO and 49/42.6 (26.4) letters in CRVO. The means (*SD*) of baseline CST (*SD*) were 511 (187) μm for BRVO and 627 (227) μm for CRVO. A higher mean CST of 722 (313) μm was found in the subgroup of 22 CRVO eyes presenting with VA ≤20 letters. Mean (*SD*) age at presentation was 72[11] years of age in BRVO and 70[13] years in CRVO. There were more males only in the CRVO cohort (67% male). Fundus fluorescein angiography was performed in 37 (27%) BRVO eyes and 20 (24%) CRVO eyes. Systemic hypertension and glaucoma were present in 74% and 7% of BRVO eyes, respectively, and 60% and 9% of CRVO eyes.

3.2 | Outcomes

The crude mean 12-month VA change (95% CI) was +14 (11.1, 16.8) letters in eyes with BRVO and + 11.9 (6.4, 17.4) letters for CRVO eyes (Table 2). Most VA improvement occurred in the first 6 months of treatment with gains of +12.5 (9.8, 15.2) letters in BRVO eyes and + 11.9 (6.4, 17.4) in CRVO eyes (Figure 1). Around 38% of eyes gained ≥15 letters (BRVO 36%, CRVO 41%). The proportion of eyes with VA > 70 letters increased from just over 20% in both groups at baseline to almost two-thirds in BRVO eyes (67%), but only one-third (33%) of CRVO eyes. CRVO eyes started with a mean VA more than

TABLE 2 Six and twelve-month outcomes all eyes, BRVO, CRVO including CRVO split into subgroups with baseline VA ≤20 and VA > 20 letters

	All Eyes	BRVO	CRVO	CRVO VA ≤ 20 letters	CRVO VA > 20 letters
Eyes	220	135	85	21	64
VA, Baseline, mean (*SD*)	50.7 (22.8)	55.8 (18.6)	42.6 (26.4)	3.2 (1.7)	55.5 (15.5)
VA, 6 months, mean (*SD*)	63.3 (20.2)	68.3 (15.4)	55.3 (24)	37.7 (26.3)	61.1 (20.3)
VA, 12 months, mean (*SD*)	63.9 (21.1)	69.8 (15.4)	54.5 (25.3)	35.1 (26.7)	60.8 (21.4)
Δ VA, 6 months, mean (CI)	12.6 (9.9, 15.3)	12.5 (9.8, 15.2)	12.8 (7.3, 18.3)	34.5 (23.3, 45.7)	5.6 (0.3, 10.9)
Δ VA, 12 months, mean (CI)	13.2 (10.4, 15.9)	14 (11.1, 16.8)	11.9 (6.4, 17.4)	32 (20.6, 43.4)	5.3 (−0.1, 10.7)
Predicted Δ VA, 12 months, mean (CI)[a]		13.6 (11.3, 15.8)	11.7 (9.0, 14.5)		
Gained 15 letters	38%	36%	41%	67%	33%
Lost 15 letters	5%	2%	11%	0%	14%
VA > 70 Baseline/12 months	21%/54%	22%/67%	20%/33%	0%/10%	27%/41%
VA ≤ 35 Baseline/12 months	23%/11%	14%/4%	36%/22%	100%/52%	16%/12%
CST, baseline, mean (*SD*)	556 (211)	511 (187)	627 (227)	730 (317)	595 (182)
CST, 6 months, mean (*SD*)	413 (166)	387 (141)	453 (193)	391 (187)	473 (192)
CST, 12 months, mean (*SD*)	384 (154)	356 (109)	429 (198)	432 (273)	428 (170)
Δ CST, 6 months, mean (CI)	−147 (−178, −117)	−130 (−164, −96)	−175 (−232, −118)	−345 (−480, −210)	−121 (−177, −65)
Δ CST, 12 months, mean (CI)	−172 (−202, −142)	−155 (−190, −121)	−198 (−252, −145)	−298 (−438, −158)	−167 (−220, −113)
Predicted Δ CST, 12 months, mean (CI)[a]		−149 (−185, −115)	−196 (−231, −161)		
Completers *n* (%)	202 (92%)	125 (93%)	77 (91%)	18 (86%)	59 (92%)
Switchers *n* (%)	40 (18%)	26 (19%)	14 (16%)	5 (24%)	9 (14%)
Non-completers *n* (%)	18 (8%)	10 (7%)	8 (9%)	3 (14%)	5 (8%)
Injections, median (Q1, Q3)[b]	7 (5, 9)	7 (5, 9)	7 (5, 9)	6 (5, 8)	7 (5, 10)
Visits, median (Q1, Q3)[b]	9 (7, 10)	8 (7, 10)	9 (7, 11)	9 (9, 11)	9 (7, 11)

Note: All Eyes—Includes completers, switchers and non-completers. 'Completers'—Eyes with 12 months of observation from the start of treatment, 'Switchers'—Eyes receiving ≥2 injections of another treatment drug prior to completion of 12 months. Observations were included in the analysis only up to the first occurrence of switching agents. 'Non-completers'—Eyes not completing 12 months of observations from the start of treatment.
Abbreviations: BRVO, branch retinal vein occlusion; CI, 95% confidence interval; CRVO, central retinal vein occlusion; CST, central subfield thickness (in microns); *n*, number; Q1, first quartile; Q3, third quartile; *SD*, standard deviation; VA, visual acuity in letters; Δ, change from baseline.
[a]Predicted outcomes calculated from longitudinal generalised additive models.
[b]Last observation carried forward for switchers and non-completers.

10 letters lower than the BRVO eyes (42.6 vs. 55.8 letters). The greatest crude gain in vision of +34.5 (23.3, 45.7) letters occurred in the 22 CRVO eyes with VA ≤20 letters at baseline, improving from count fingers (CF) or 3 (1.7) letters to 37.7 (26.3) letters. Three-line losses of vision occurred more in CRVO eyes (8 eyes, 11%) than BRVO eyes (3 eyes, 2%). Twenty-five eyes (11%) had a final VA ≤35 letters (6/60) after 12 months (6 BRVO eyes, 19 CRVO eyes).

The crude mean (*SD*) changes in CST in BRVO of −155 (−190, −121) μm, and in CRVO of −198 (−252, −145) μm at 12 months (Figure 1, Table 2). Mean CST (*SD*) was higher in CRVO eyes than in BRVO eyes at baseline [627 (227) μm/511 (187) μm], at 6-months [453 (193) μm/387 (141) μm], and at 12-months [429 (198) μm/356 (109) μm], respectively. The CRVO eyes with VA ≤20 letters had the highest CST at baseline [730 (317) μm] and the greatest crude change in CST over 12 months of −298 (−438, −158) μm.

3.3 | Treatments and visits

BRVO completers (92%) had a median (Q1, Q3) of 7[5,9] injections over 8[7,10] visits, similar to CRVO completers (91%); 7[5,9] injections and 9[7,11] visits (Table 2). Mean injections given between 6 and 12 months was 2.4 in both BRVO and CRVO eyes. Thirty-one eyes (14% of completers) had fewer than four injections with a median final VA of 71 letters. Macular laser at a median of 175 days was applied to 7 BRVO eyes (5%). Cataract surgery was performed in three eyes (2 BRVO and 1 CRVO).

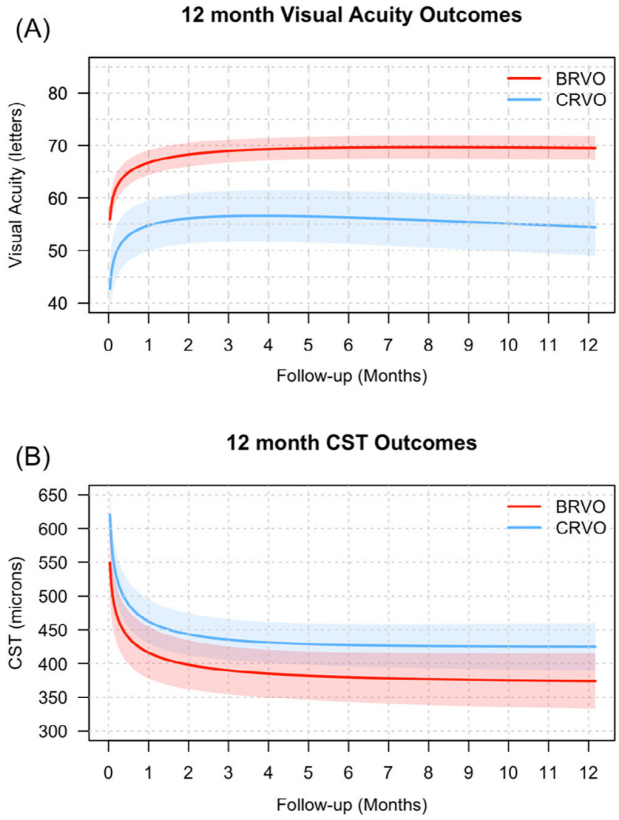

FIGURE 1 12-month Visual acuity (VA) and central subfield thickness (CST) outcomes treating BRVO and CRVO with bevacizumab therapy. Shading indicates confidence intervals surrounding mean predicted VA and CST

3.4 | Inactivity, switching and non-completion

Kaplan–Meier survival curves, and log-rank tests demonstrated no difference in time to first grading of CMO inactivity between RVO types ($p = 0.6$), switching ($p = 0.6$) and non-completion ($p = 0.6$) for BRVO versus CRVO treated with bevacizumab over 12 months (Figure 2). Ninety-four BRVO eyes (69%) and 56 CRVO eyes (65%) recorded one or more visits with no CMO activity. The first grading of inactivity was at a median (Q1, Q3) of 84 (38, 191) days (Figure 2).

Forty eyes (18%) switched treatment within 12 months (Table 2). Switching occurred in 26 eyes BRVO (all in Australia) at a median (Q1, Q3) of 224 (163, 306) days and VA of 72 (63, 77) letters; aflibercept (11 eyes), IVTA/Ozurdex (2 eyes) or to ranibizumab (13 eyes). Switching occurred in 14 CRVO eyes (13 in Australia) at a median (Q1, Q3) of 143 (114, 216) days and VA of 55 (40, 60) letters; aflibercept (7 eyes), IVTA (2 eyes), ranibizumab (5 eyes). The four eyes that switched to steroid had mean VA of 52 (51, 75) letters at 217 (126, 273) days when they switched. Eighteen eyes (10 BRVO and 8 CRVO) dropped out at a median time of 166 (130, 211) days with median VA of 75 (69, 79) letters.

3.5 | Adverse events

Macular changes affecting vision were noted in 10 eyes at baseline (pigment clumping, atrophy, epiretinal membrane, macular hole) with a median VA (*SD*) at 12 months of 50[24] letters (6/24), including 2 of the 10 eyes that lost ≥15 letters, and 4 of the 25 eyes that had a final VA of ≤6/60. Panretinal or sector photocoagulation was performed in 37 eyes (26 BRVO and 11 CRVO). Vitreous haemorrhage occurred in three eyes; all managed without vitrectomy. There was one reported case of non-infectious endophthalmitis with a baseline VA of 11 letters and final VA of CF, but no traumatic cataract or retinal detachment from a total of 1507 injections.

4 | DISCUSSION

This analysis of prospectively collected observational data demonstrates that in a real-world setting, bevacizumab can be effective at improving vision in patients with MO secondary to RVO. The crude mean improvement in VA in eyes with BRVO and CRVO was 14.0 and 11.9 letters, respectively, with most of this improvement occurring in the first 6 months of treatment. These outcomes were achieved with a median of seven injections being administered for both BRVO and CRVO. Eyes with CRVO had a thicker mean CST at baseline (627 vs. 511 μm BRVO), but both groups achieved a significant improvement with treatment at 12 months (356 μm BRVO, 429 μm CRVO). Most BRVO and CRVO eyes experienced a significant improvement in vision regardless of the presenting VA.

A recent systematic review of RWS on the management of DMO and RVO-related MO indicated that visual and anatomical gains achieved often fall short of those achieved in RCTs, with suboptimal results likely stemming from reduced treatment frequency and differences in study population demographics and clinical parameters.[15–17] The gains in VA and CST observed in our real-world BRVO cohort using bevacizumab were however only marginally inferior to those of the landmark RCTs which used ranibizumab and aflibercept (Table 3).[18–20] Whilst we should be cautious in comparing study outcomes, the observation that 38% of eyes in our BRVO cohort were still active at any visit suggests a degree of undertreatment. This may explain the inferior results we report. The observation that only seven injections were delivered in the current study over

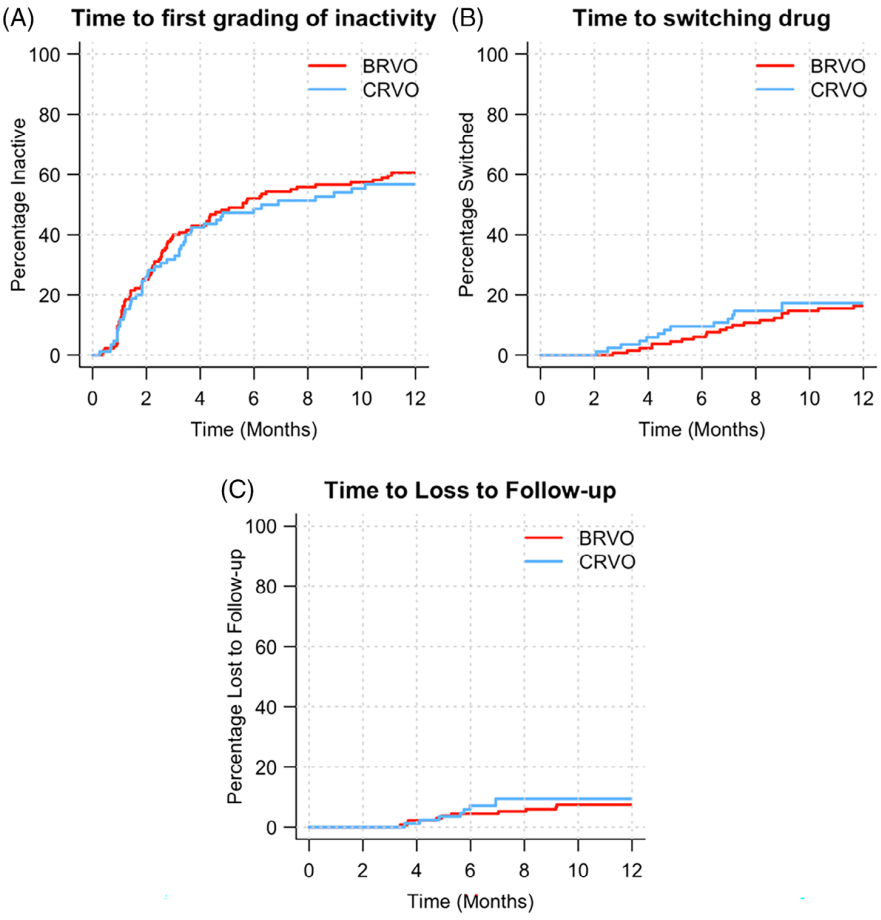

FIGURE 2 Kaplan–Meier curve for (A) first grading of inactivity, (B) time to switching and (C) dropout by BRVO (red) or CRVO (blue)

12-months, compared with the 8–10 injections delivered in RCTs further supports this hypothesis.

The improvement in VA in eyes with BRVO achieved in this current study is similar to those reported by other RWS which achieved a similar treatment frequency, irrespective of which anti-VEGF agent was used.[6,21] These data suggest that, at least for BRVO, the choice of anti-VEGF used may have less influence on treatment outcomes than the frequency of treatment. This hypothesis is supported by the recent analysis of eyes with BRVO in the FRB! registry which were treated with either ranibizumab or aflibercept.[3] The mean change in VA from a similar mean baseline in this RWS (+10.9 letters) was comparable to that observed in the current study with a similar number of injections having been administered (median also seven). Similarly, the mean CST improvement for BRVO eyes in our study of −149 μm was within the range reported in the cohorts treated with aflibercept (−170 μm) or ranibizumab (−147 μm).

CRVO is regarded as a separate, more severe disease entity than BRVO with generally worse patient outcomes. Compared with both CRUISE and COPERNICUS (Table 3),[22,23] eyes with MO secondary CRVO in the current study recorded inferior improvements in VA, (11.9 vs. 13.9 and 16.2 letters, respectively), despite presenting with worse vision. CST at baseline was comparable between CRUISE [689 μm (0.5 mg)], COPERNICUS (662 μm) and our study cohort (627 μm), but eyes in the current study had less improvement in CST (−198 μm) at 12 months compared with that observed in both CRUISE and COPERNICUS (−462 vs. −413.0 μm). As 54% of eyes in the current study were active at every visit it is again likely that undertreatment explains the poorer VA and CST results in our CRVO cohort compared with the landmark RCTs as both CRUISE and COPERNICUS had prescriptive treatment regimens which delivered more injections compared to the current study (9.3, 8.7 vs. 7). The mean VA gain in CRYSTAL, which delivered fewer treatments than did CRUISE (mean treatments 8.1 vs. 9.3), was 12.3 letters,[24] similar to the present study. However, patients enrolled in CRYSTAL had a significantly higher baseline mean VA than those in our cohort with CRVO, which may have imposed a ceiling effect on their potential gains. That they achieved a significantly

TABLE 3 Comparison of study results against RCTs and RWS for BRVO and CRVO

	Baseline VA (LogMAR letters)	12-month VA gain (LogMAR letters)	Total injections over 12-months
Our study results: BRVO	55.8	+14.0	7
BRAVO: Rbz (RCT)[20]	54.6	+18.3	8.5 (0.3 mg)/8.4 (0.5 mg)
VIBRANT: Afl (RCT)[18]	58.6	+17.1	9.0
BRIGHTER: Rbz (RCT)[19]	59.5	+15.4	11.4 (24 months)
FRB!: Rbz/Afl (RWS)[3]	55.6	+10.8/+10.9	7
BERVOLT-BRVO: Bvz (RWS)[6]	46.0	+13.0	7.6 (24 months)
OCEAN-BRVO: Rbz (RWS)[21]	55.9	+13.1	4
Our study results: CRVO	42.6	+11.9	7
CRUISE (RCT)[22]	48.3	+13.9	5.8 (0.3 mg)/5.5 (0.5 mg)
COPERNICUS (RCT)[23]	50.0	+16.2	8.7
CRYSTAL[24]	53.0	+12.3	8.1
LEAVO: Rbz/Afl/Bvz (RCT)[7]	54.1	+12.5/+15.1/+9.8 (100 weeks)	11.8/10.0/11.5 (100 weeks)
FRB!: Rbz/Afl (RWS)[25]	36.9/42.5	+9.8/+16.6	7
BERVOLT-CRVO: Bvz (RWS)[6]	28.0	−4.0	9.6 (24 months)
OCEAN-CRVO: Rbz (RWS)[21]	43.9	+4.1	5

Abbreviations: Afl, aflibercept; Bvz, bevacizumab; Rbz, ranibizumab; RCTs, randomised controlled trials; RWS, real-world setting.

greater reduction in mean CST of −335.6 μm, compared with −198 μm observed in our CRVO patients, suggests this may be the case.[24]

The results from our CRVO cohort are better than those reported by other RWS. The CRVO cohort of BERVOLT actually reported a decrease in VA at 12 months, whilst CRVO eyes in OCEAN only achieved +4.1 letters over a 1-year period.[6,21] Undertreatment likely explains the disappointing results of these other RWS. Whereas eyes in BERVOLT received only 7.6 injections over 24 months and those in OCEAN received a median of just 5,[6,21] eyes with CRVO in the current study received a median of seven injections in 12 months with correspondingly better visual outcomes, thereby demonstrating that an adequate number of injections can be given to eyes with CRVO in routine clinical practice.

Whilst it is again very likely that the primary determinant of treatment outcomes in CRVO is treatment frequency, differences between the efficacy of the three VEGF inhibitors may also be important. LEAVO reported an improvement in BCVA of +12.5 for ranibizumab for CRVO, +15.1 for aflibercept compared to just +9.8 letters for bevacizumab.[7] The authors concluded that, when adjusted for all other factors, bevacizumab was not non-inferior to aflibercept. Data recently published from the FRB! registry reported that eyes with CRVO treated with aflibercept (16.6 letters) had significantly greater 12-month visual gains than eyes treated with than ranibizumab (9.8) (Table 3).[25] This compares with the observed mean VA gain of 11.9 letters in eyes treated with bevacizumab in the current study. Whilst direct comparison is not possible, these data suggest that, unlike BRVO, the choice of anti-VEGF also may also influence the treatment outcome for patients presenting with MO secondary to CRVO. *Further studies comparing bevacizumab to ranibizumab and aflibercept in a real-world setting would be helpful.*

Approximately 20% of eyes in both the BRVO and CRVO cohorts switched agents over the course of the study and in most cases this was to another VEGF inhibitor. Most switchers were in the Australian cohort. As the decision to switch agents is at the clinicians' discretion and this decision is not documented in FRB! we cannot determine if switching was a result of a poor response to bevacizumab or due to changes in how the Australian Federal government reimbursed anti-VEGF treatments starting in 2016. The observation that the mean VA at time of switching in BRVO was 72 letters nevertheless suggests that individuals with BRVO were switched for reasons other than treatment efficacy. No conclusion can be drawn from the CRVO cohort as the mean VA at time of switching in CRVO was lower at 55 letters. The change in funding could also have affected the clinicians' choice of agent when commencing treatment as aflibercept and ranibizumab were subsidised only if the presenting vision was >20 letters for BRVO or > 24 letters for CRVO. Australia contributed 67% of all eyes in the analysis that commenced bevacizumab treatment before January 2016 but only 23% of CRVO eyes and 30% of BRVO eyes after January 2016. The median (Q1, Q3) baseline VA and CST

in Australian CRVO eyes was worse after January 2016 dropping from 43 (23, 58) letters and 585 μm to 33 (3, 45) letters and 845 μm. This suggests that many eyes in the Australian cohort commenced on bevacizumab after 2016 were those with worse CRVOs which did not fulfil the funding criteria for other anti-VEGF agents. This raises the possibility that there is a selection bias in our CRVO cohort with those patients with ischaemic CRVO being overrepresented. It is unlikely that a similar bias was present in the BRVO cohort as the baseline characteristics of BRVO eyes in Australia were not different before and after 2016.

This study used observational data from a real-world database so there are the usual limitations that apply to RWS. Clinical judgement and patient preferences would influence the decision-making process. However, adherence to treatment in this cohort was excellent with 93% of individuals with BRVO and 89% of those with CRVO completing 12 months.

In conclusion, our study found that bevacizumab can achieve good visual outcomes for both BRVO and CRVO in a real-world setting which are only slightly inferior to those reported by the landmark RCTs of ranibizumab and aflibercept. This is most likely due to less aggressive treatment resulting in suboptimal reductions in CST. Our findings were, however, generally better than those of other RWS, which tended to treat less aggressively.[6,21]

Although a detailed cost analysis comparing the efficacy of the various anti-VEGFs agents for treating RVO is beyond the scope of the current study, our findings support the first-line use of bevacizumab for RVO in health economies with limited financial resources.

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CONFLICT OF INTEREST

ILM and MCG are members of advisory boards for Novartis and Bayer. MCG is also a member of an advisory board for Allergan. ARH and MCG 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.

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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.

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.

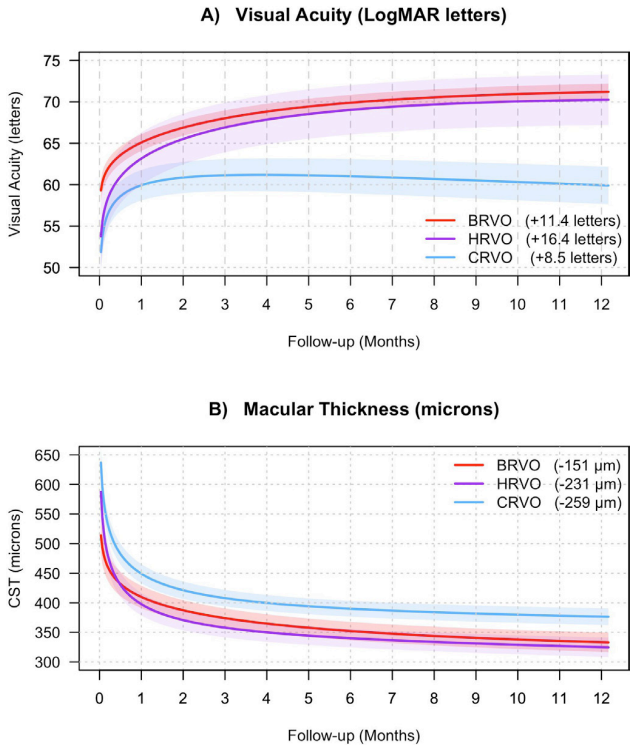

Figure 1 (A) Mean visual acuity and (B) Macular thickness over 12 months by RVO type. The HRVO group started with mean VA and CST more like the CRVO group but soon resembled the BRVO group. Shading indicates 95% CIs. The legend has the 12 months mean changes from baseline in VA and CST in parentheses. 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

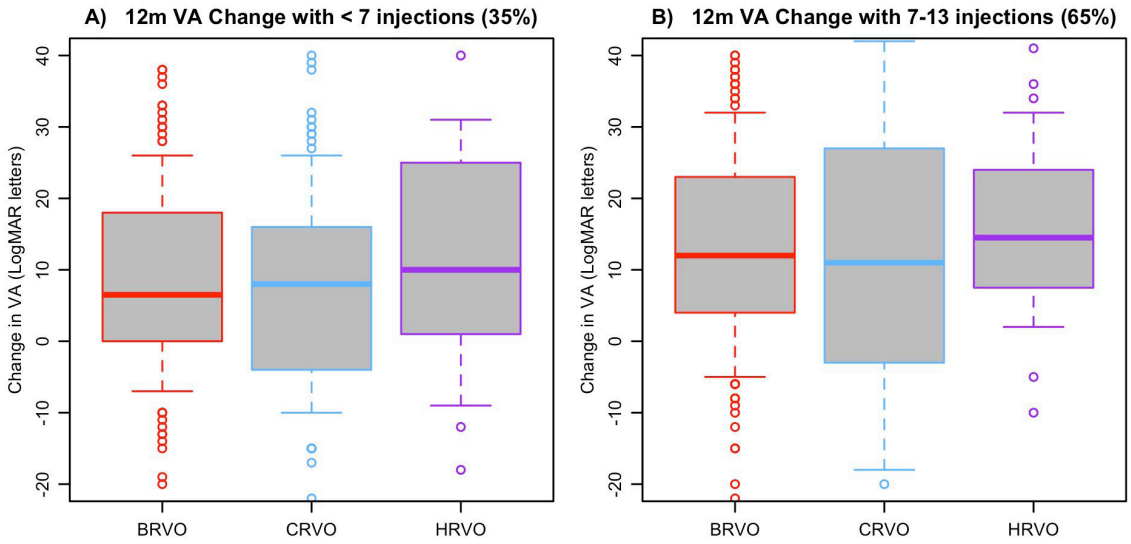

Figure 2 Boxplot of change on VA at 12 months with (A) <7 injections (35% of completers) or with (B) 7–13 injections (65% of completers). The boxes (first to third quartiles) contain median (bold line) with whisker extension at 50% of the IQR. BRVO, branch RVO; CRVO, central RVO; HRVO, hemiretinal vein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

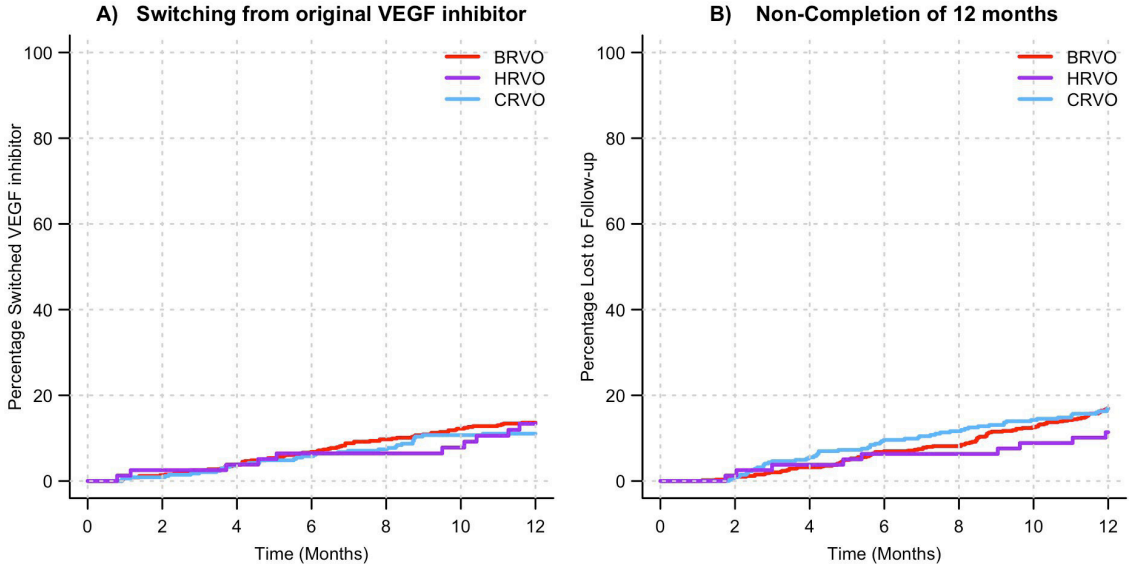

Figure 3 Kaplan-Meier survival curves describing time to (A) switching from original VEGF inhibitor and (B) non-completion by RVO type. BRVO, branch RVO; CRVO, central RVO; HRVO, hemiretinal vein occlusion; VEGF, vascular endothelial growth factor.

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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Central Retinal Vein Occlusion 36-Month Outcomes with Anti-VEGF

The Fight Retinal Blindness! Registry

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Purpose: To analyze the 3-year outcomes in a broad population of patients starting VEGF inhibitors for central retinal vein occlusion (CRVO) in routine clinical practice.

Design: Observational database study.

Participants: Overall, 527 treatment-naïve CRVO eyes that commenced VEGF inhibitors between December 1, 2010 and 2018 were tracked in the Fight Retinal Blindness! registry.

Methods: Longitudinal models were used to plot changes in visual acuity (VA) and central subfield thickness (CST).

Main Outcome Measures: Mean change in VA from baseline to 36 months, injections, visits, completion, switching, and suspensions of therapy $>$ 180 days at the final review.

Results: Overall (527 eyes) mean VA change (95% confidence interval [CI]) was $+$ 10 (7, 12) letters, 37% had final VA $\geq$ 70 and 30% $\leq$ 35 letters, mean CST changed $-$306 μm. Completers (257/527, 49%) had mean 36-month changes in VA and CST of $+$ 12 letters and $-$324 μm with a median of 18 injections at 26 visits. The adjusted mean VA change was similar to each VEGF inhibitor (mean, $+$ 11.4 letters) despite a greater reduction in CST with aflibercept ($-$310 μm) versus ranibizumab ($-$258 μm) versus bevacizumab ($-$216 μm; $P < 0.001$). Eyes with baseline VA that was trial-eligible (19$-$73 letters; 356/527, 68%) gained 7 letters, very poor ($<$ 19 letters; 129/527, 24%) gained 22 letters, or very good ($>$ 73 letters; 42/527, 8%) lost 7 letters. Switching (160/527, 30%) was most often to aflibercept (79 eyes). By using suspensions and discontinuation reasons, we identified similar proportions had ceased therapy (154/527, 29%) and were still receiving it at 36 months (165/527, 31%). Only 62/527 eyes (12%) had resolution of macular edema without treatment for $>$ 6 months.

Conclusions: Patients with CRVO that commenced VEGF inhibitors in routine care for whom follow-up was available had VA improvements of around 12 letters at 3 years, but with $>$ 50% lost to follow-up, the VA outcome for the entire group was likely worse. The choice of VEGF inhibitor influenced CST but not VA outcomes. We estimated that around half of the eyes were still receiving injections after 36 months.

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VEGF inhibitors are recommended as first-line treatment of cystoid macular edema (CME) because of central retinal vein occlusion (CRVO).[1,2] This is based on the overwhelming safety and efficacy of ranibizumab and aflibercept reported in pivotal randomized clinical trials (RCTs).[3–9] Bevacizumab is an "off-label" alternative VEGF inhibitor listed on the World Health Organization list of essential medicines with similar outcomes to approved agents when compared by RCTs at 2 years.[10–12] Outcomes beyond 2 years are less clear because there are few patients enrolled in extension studies that followed the RCTs. This is where evidence derived from routine care can help, but few studies have significant follow-up.

Existing evidence fails to account for many patients with CRVO who may experience disease resolution or who abandon therapy within a few years of starting it. A large study extracted measurements from the medical records of 3577 patients with CRVO treated with VEGF inhibitors in the United Kingdom but had visual acuity (VA) in only 6% of eyes at 3 years.[13] Smaller retrospective studies often

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avoid the problem of variable follow-up by performing "completers-only analyses" only studying eyes with a requisite period of observation, such as 3 or 5 years.[14–16]

Few eyes participated in long-term extension studies that followed pivotal RCT. The RETAIN study[17] (macular edema because of b*R*anch r*ET*inal vein occlusion or CRVO previously treated with intravitreal ranibizumab) is often cited in discussions regarding long-term outcomes of VEGF therapy in CRVO. It concluded that around half of the eyes still required treatment at 4 years. The sample enrolled in the RETAIN extension study consisted of 8% of participants from CRUISE (ranibizumab for the treatment of macular edema after CRVO study) but was found to be representative of the original cohort.[18]

Our objective was to study 3-year outcomes in a broad population of patients starting VEGF inhibitors for CRVO in routine care—with particular interest in visual outcomes, number of injections, and need for ongoing treatment—by analyzing data from the retinal vein occlusion module of the Fight Retinal Blindness! (FRB!) registry.

Methods

Design and Settings

This was a retrospective observational study using anonymized data obtained from the retinal vein occlusion module of the FRB! registry.[19] Treatment decisions were made at the discretion of the physician and patient during routine clinical practice. Data points were numeric, drop-down lists, or mutually exclusive. These included VA in letters (best of uncorrected, corrected, or pinhole) using a logarithm of the minimum angle of resolution chart, central subfield thickness (CST [μm]) assessed with OCT using the same machine for the same patient throughout, treatments given, and adverse events. The baseline visit, defined by the first injection, required entry of additional data regarding demographics, the type of RVO (central, branch, or hemiretinal), and presence of key risk factors.

Ethics and data protection approval was granted in Australia and New Zealand—Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09); United Kingdom—Caldicott Guardian (Until Sept 2024); Ireland—Mater Private Hospital (IRB, 1/378/2130); Spain—Comité Etico de Investigación Medica, Hospital Clínic de Barcelona (2015/57-OFT-HUSC); Italy—IRCCS Ca Granda Foundation Maggiore Policlinico Hospital; France—Société Française d'Ophtalmologie (2017_CLER-IRB_ll-05). Patients gave their informed consent, which was "opt-in" in European centers and "opt-out" in Australia and New Zealand, as approved by local ethics committees. Because of the noninterventional nature of the registry, the Medical Ethics Committees in Italy and the Netherlands ruled that approval was not required for this study. The study adhered to the tenets of the Declaration of Helsinki and strobe checklists for reporting observational studies.[20]

Patient Selection and Definitions

We included treatment-naïve patients with CME because of CRVO that commenced treatment with either bevacizumab (1.25 mg Avastin; Genentech, Inc), ranibizumab (0.5 mg Lucentis, Genentech Inc/Novartis), or aflibercept (2 mg Eylea, Bayer) between December 1, 2010 and December 1, 2018. Branch and hemiretinal vein occlusions were excluded. The study included the first treatment visit until the 36-month visit closest to 1095 ± 30 days. "Completers" were defined as having follow-up ≥ 1065 days. Treatment during the 3-year study was either "Monotherapy" with the original VEGF, "VEGF-switched" (≥ 2 alternate VEGF injections), or "steroid-switched" (≥ 1 steroid injection). "Suspension" of therapy was defined as a period of observation that contained ≥ 1 visits without therapy spanning > 180 days, either concluding at the final review or with resumption of therapy within the 3-year study.

Outcomes

The primary outcome was the mean change in VA from baseline to 36 months. Secondary outcomes included percentage of eyes with final VA ≥ 70, VA ≤ 35 letters, VA gain or loss ≥ 15 letters; mean change in CST; frequency of visits and injections; suspensions of therapy; noncompletion; switching; and adverse events. The FRB! project collects a prospectively defined, minimum, patient-centered outcomes set with mandatory fields, so all data analyzed were 100% complete and within prespecified ranges.

Statistical Analysis

Data were summarized where appropriate with counts, percentages, means, standard deviations (SDs), 95% confidence intervals (CIs), medians, and first and third quartiles (Q1, Q3). Because we observed high rates of switching and noncompletion, we considered it inappropriate to compare VEGF agents based on unadjusted outcomes in the select eyes that were monotherapy completers. Instead, we used generalized additive mixed effects models to predict VA and CST outcomes with VEGF inhibitors combined (censoring if "steroid-switched"); separately, we compared response with individual VEGF inhibitors (censoring if "VEGF-switched" or "steroid-switched"), adjusting for baseline age and baseline VA (or CST) as fixed effects. Nesting of outcomes within practice and eyes from the same patient were considered random effects.

Unadjusted outcomes were reported without censoring after switching with grouping by treatment received (Monotherapy, VEGF-switched, or steroid-switched), using the last observation carried forward in noncompleters. Supplementary analyses included outcomes in switchers and by baseline VA according to the inclusion criteria of major trials[4,7,9,11,18,21] (*very-poor* < 19 letters, *trial-eligible* 19—73 letters, or *very-good* > 73 letters). Kaplan—Meier survival curves were generated for switching and noncompletion with the drugs compared using Cox-proportional hazard models.

Statistical analysis was performed using the R version 4.1.3 (http://www.R-project.org/) utilizing the *mgcv* (V1.8-35) and *itsadug* (V2.4) packages for generalized additive mixed effects models, the *survival* (3.3-1) package to generate the Kaplan—Meier estimates, and *coxme* (2.2-16) for comparing event-based outcomes by drug.[22]

Results

Patient Characteristics and Disposition

We identified 527 treatment-naïve eyes with CME because of CRVO that started VEGF inhibitors between December 1, 2010, and December 1, 2018 (Table 1). Baseline mean (SD) age was 71 years (12), mean VA was 41 letters (25), and mean CST was 641 μm (233) overall. Demographics were broadly similar between groups whether stratified by initial VEGF inhibitor (128 [24%] bevacizumab, 227 [43%] ranibizumab, or 172 [33%] aflibercept)

or by the treatment received over 3 years (366 [68%] monotherapy, 98 [19%] VEGF-switched, and 63 [12%] steroid-switched) (Tables S1 and S2, available at www.ophthalmologyretina.org). Baseline characteristics of eyes that completed 36-month follow-up (257 [49%]) or noncompleted 36 months (270 eyes [51%]) are described in Table S3 (available at www.ophthalmologyretina.org).

Visual and Anatomic Outcomes

Overall, the mean VA change (95% CI) was + 10 letters (7, 12) and mean CST change was −306 μm (−329, −282); mean final VA was 51 letters; 44% of eyes gained and 14% lost ≥ 15 letters; 37% had VA ≥ 70 letters; and 30% had VA ≤ 35 letters (Table 2). Two-thirds of eyes received their original monotherapy only (366 [69%]). Eyes that switched between VEGF agents (98 [19%]) had similar VA gains (+ 11 letters) to eyes that received monotherapy (+ 11 letters), but with more injections (20 versus 10 injections, respectively; $P < 0.001$) and persisted longer (76% versus 42%, 36-month completion rate, respectively). Eyes that switched to steroid (63 [12%]), including triamcinolone in 14 eyes or dexamethasone implant in 49 eyes, had negligible change in vision over 3 years and underwent cataract surgery during the study more often (27%) than eyes not treated with steroids (11%; $P = 0.002$).

Completers (257/527 [49%]) had mean 36-month VA change (95% CI) of + 12 letters (9, 15) and mean CST change of −324 μm (−358, −291). The monotherapy 36-month completers (152 [29%]) had the highest mean change in VA of + 14 letters (Table 2), but different rates of switching and noncompletion made the original VEGF inhibitor groups unrepresentative by 36 months. We used longitudinal models to adjust and plot outcomes with VEGF inhibitors combined (Fig 1). At 2 months mean VA peaked at 56.6 letters (+ 15.5 letters from baseline) and mean CST reduced to 367 μm (−247 μm from baseline). At 36 months, the mean change in VA had decreased from the peak by 4 letters (+ 11.4 letters from baseline) despite a further 40 μm reduction in mean adjusted CST (−287 μm from baseline). Our models found no differences based on VEGF inhibitor in adjusted VA beyond the first year of the study (Fig S2, available at www.ophthalmologyretina.org); however, a distinct order of efficacy in reducing CST was found throughout the study in favor of aflibercept over ranibizumab over bevacizumab ($P < 0.001$; Fig S2).

Outcomes grouped by baseline VA are described in Table S4 (available at www.ophthalmologyretina.org). The two-thirds (356 [68%]) with *trial-eligible* baseline VA (19−73 letters) had mean VA change (95% CI) of + 7 (5, 10) letters, mean CST change of −285 μm (−311, −259), final VA in 44% was ≥ 70 letters, 19% ≤ 35 letters, and they received a median of 13 injections. The quarter (129 [24%]) with *very-poor* baseline VA (< 19 letters) had large mean VA and CST changes (+ 22 letters, −448 μm), fewer injections (median, 7), lower completion rates (37%), and most (70%) had final VA ≤ 35 letters. The 44 eyes (8%) with baseline VA > 73 letters, on average, lost some vision (mean, −7 letters), had smaller changes in CST (−121 μm), more injections (median, 15), higher completion rates (67%), and the majority (67%) had final VA ≥ 70 letters.

Treatments and Visits

The 36-months completers (257 eyes [49%]) had a median of 18 (13, 24) injections and 26 visits in 3 years (Table 2). Eyes that completed 1, 2, and 3 years had a mean of 7.6, 4.9, and 4.2 injections in each of those years, respectively. The entire cohort received a median (Q1, Q3) of 12 (6, 19) injections, with 20 (13, 28) visits during the study. One-third of eyes (182/527 [34%]) were treated with panretinal photocoagulation; these eyes had lower mean baseline VA (32 letters) and lower mean final VA (35 letters) but no significant difference in the frequency of injections ($P = 0.74$) than the eyes that did not receive panretinal photocoagulation. We found no difference in outcomes, including injections and visits, in eyes commencing treatment in 2018 that were in part managed during the coronavirus disease 2019 pandemic (2020).[23]

Suspension of therapy lasting > 180 days occurred in 223 of 527 eyes (42%) during the 3-year study. In 141 eyes (27%, 62 completers, 79 noncompleters), the suspension continued to final review, VA and CST changed little after ceasing treatment (mean, + 2 letters, −41 μm), and mean final VA change was + 11 letters from baseline, but the final VA had a bimodal distribution (40% ≥ 70 letters, 41% ≤ 35 letters). Only 65 (12%) eyes suspended with CST consistently remained < 300 μm, also with a bimodal distribution of final VA (48% ≥ 70 letters, 37% ≤ 35 letters).

In 82 eyes (15%), the suspension was only temporary, during which there was a deterioration in mean VA of −9 letters (from 58−49 letters) and CST of + 51 μm (from 360−411 μm). Despite restarting treatment, mean final VA change was only + 2 letters from baseline in these eyes.

Predicting outcomes of noncompleters required inference, while acknowledging that some patients likely continued to receive therapy outside the registry. We used suspensions (27%) as the marker for cessation; however, many noncompleters were not followed for 6 months after their last recorded injection to qualify (mean follow-up after last injection, 149 days). Treatment between 30 and 36 months was documented in 195 completers (37%), however, when we accessed all available follow-up, 33 of these eyes (6%) had no further treatment after their last injection

Table 1. Baseline Demographic Characteristics of Patients Included in the Study

Eyes, n	527
Patients, n	516
Initial VEGF inhibitor	
Bevacizumab, n (%)	128 (24)
Ranibizumab, n (%)	227 (43)
Aflibercept, n (%)	172 (33)
Female, % patients	42%
Age, mean (SD)	71 (12)
VA, mean (SD) letters	41 (25)
Very-poor VA < 19 letters, n (%)	129 (24)
Trial-eligible VA 19−73 letters, n (%)*	356 (68)
Very-good VA > 73 letters, n (%)	42 (8)
CST, mean (SD), μm	641 (233)
Pseudophakia, %	21%
Hypertension, %	61%
Glaucoma, %	16%

CST = central subfield thickness; n = number; SD = standard deviation; VA = visual acuity.
*Stratification by baseline VA based on inclusion criteria of major trials (typically 19−73 letters).[4,7,9,11,18,21]

Table 2. Thirty-Six Months Outcomes in All Eyes and Based on Treatment Received

	All Eyes	Monotherapy	VEGF-Switched	Steroid-Switched
Eyes, n, (% entire cohort)	527 (100)	366 (69)	98 (19)	63 (12)
VA baseline, mean (SD)	41 (25)	41 (26)	42 (25)	38 (26)
VA final, mean (SD)	51 (29)	52 (29)	54 (25)	38 (28)
VA change, mean (95% CI)	+10 (7, 12)	+11 (8, 13)	+11 (6, 17)	0 (−7, 7)
Gain ≥ 15 letters, %	44%	45%	49%	29%
Loss ≥ 15 letters, %	14%	12%	16%	25%
VA ≥ 70% Baseline%/Final%	15%/37%	14%/40%	16%/37%	16%/19%
VA ≤ 35% Baseline%/Final%	40%/30%	39%/30%	43%/22%	43%/46%
CST baseline, mean (SD)	641 (233)	630 (234)	676 (242)	654 (211)
CST final, mean (SD)	335 (154)	320 (140)	343 (170)	414 (182)
CST change, mean (95% CI)	−306 (−329, −282)	−310 (−337, −283)	−333 (−394, −273)	−240 (−315, −166)
Injections, median (Q1, Q3)	12 (6, 19)	10 (5, 17)	20 (13, 26)	12 (7, 15)
Visits, median (Q1, Q3)	20 (13, 28)	17 (10, 25)	28 (21, 32)	24 (16, 32)
Suspension at final review, n (%)*	141 (27)	116 (32)	15 (15)	10 (16)
Panretinal photocoagulation, n (% column)	182 (34)	106 (29)	42 (43)	34 (54)
Elevated IOP requiring treatment, n (% column)	16 (3)	10 (3)	2 (2)	4 (6)
Cataract surgery performed, n (% column)	69 (13)	41 (11)	11 (11)	17 (27)
36-Month completers, n (% column)	257/527 (49)	152/366 (42)	74/98 (76)	31/63 (49)
VA Change in Completers, mean (95% CI)	+12 (9, 15)	+14 (11, 18)	+13 (7, 19)	+1 (−9, 11)
CST change in completers, mean (95% CI)	−324 (−358, −291)	−341 (−383, −299)	−345 (−408, −281)	−196 (−300, −92)
Injections in completers, median (Q1, Q3)	18 (13, 24)	16 (10, 22)	22 (17, 27)	18 (15, 21)
Visits in completers, median (Q1, Q3)	26 (22, 32)	24 (19, 29)	30 (25, 33)	30 (24, 36)

All eyes—outcomes without censoring observations after switching and using last observation carried forward in noncompleters, Monotherapy—eyes treated with initial vascular endothelial growth factor inhibitor only, VEGF-switched—≥ 2 alternate VEGF injections, steroid-switched—≥ 1 steroid injection.
CI = confidence interval; CST = central subfield thickness; IOP = intraocular pressure; n = number; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; VA = visual acuity.
*No treatment observed for > 180 days leading up to final review.

during the final 6 months of the study. When combined with reasons given for discontinuation (below) that indicated cessation, we established treatment status (ongoing or ceased) in 319 (61%) of 527 of participants. One hundred sixty-five patients (31%) were still requiring treatment at 3 years and 154 patients (29%) had concluded treatment before 3 years.

Switching

Switching occurred in 160 eyes (30%). Switching rates differed significantly from the initial VEGF inhibitor (bevacizumab 43%, ranibizumab 38%, and aflibercept 11%; $P < 0.001$, Fig 2). Half of all switchings were to aflibercept (79 eyes, 15%). Two strong patterns of VEGF switching reflected increasing availability of drugs during the study: from bevacizumab (29/128, 23%) to ranibizumab and from ranibizumab (68/227, 30%) to aflibercept. Specific switching outcomes are described in Table S5 (available at www.ophthalmologyretina.org).

Noncompletion of 36 Months

Noncompleters (270/527, 51%; Table S6, available at www.ophthalmologyretina.org) had mean VA change (95% CI) of + 7 (4, 10) letters and mean (SD) final VA 45 letters (30); 39% gained ≥15 letters, 17% lost ≥ 15 letters; 32% had VA ≥ 70 letters, 38% had VA ≤ 35 letters and mean change in CST was −288 μm after a median (Q1, Q3) of 7 (4, 12) injections over 18 (12, 26) months. Noncompletion rates were higher with aflibercept ($P = 0.001$, Fig 2), but aflibercept noncompleters had a higher mean VA change (+ 10 letters) than ranibizumab (+ 6 letters) or bevacizumab (+ 7 letters) noncompleters ($P = 0.003$). Noncompletion was associated with higher baseline age ($P = 0.03$), lower baseline VA ($P = 0.005$), and lower baseline CST ($P = 0.02$, Table S3).

Discontinuation reasons were available in 102 eyes (38% of 270 noncompleters): 39 transferred care to another physician, 5 had "treatment successful," 14 "declined treatment," 2 had "medical contraindications," and in 8 "further treatment was futile" and 34 patients died on active treatment.

Adverse Outcomes

New macular changes were recorded in 67 (13%) eyes (epiretinal membrane, macular hole, pigment clumping, or atrophy). Neovascular complications occurred in 68 (13%) eyes, including rubeotic glaucoma in 22 (4%) eyes. Eyes with *very-poor* baseline VA (< 19 letters) more often had neovascular complications (31%; $P < 0.001$) or macular changes (25%; $P < 0.001$). There was 1 retinal detachment (final VA, 85 letters), 1 case of infectious endophthalmitis (count fingers), and 2 cases of noninfectious endophthalmitis (51 and 79 letters) after a total of 7022 injections in the study.

Discussion

We analyzed data from the FRB! observational database to describe 3-year outcomes in 257 eyes for which data were available out of a total of 527 treatment-naïve CRVO eyes commenced on aflibercept, ranibizumab, or bevacizumab in routine clinical practice. In this portion of eyes with follow-up out of a broad cohort derived from routine care, the overall mean change in VA at 36 months was + 12 letters,

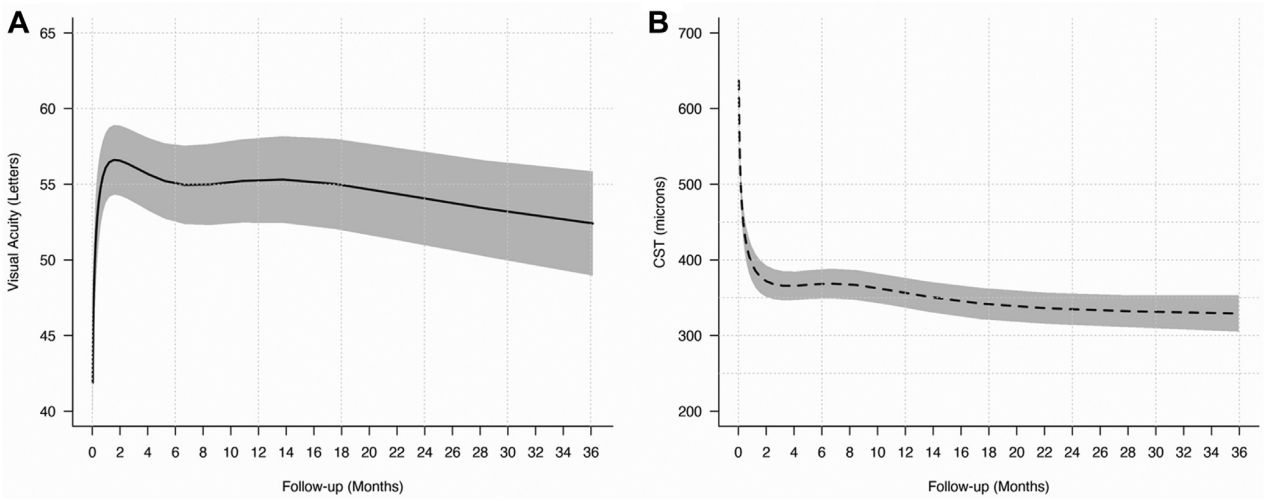

Figure 1. Predicted mean visual acuity (VA) and central subfield thickness (CST) with VEGF inhibitors (combined) over 3 years with observations censored only if patients "steroid-switched" (**A**) predicted VA and (**B**) predicted CST in an average patient from our cohort with mean age (71 years) starting with mean baseline VA (41 letters) and CST (641 μm). The shading represents the confidence intervals of the predicted means.

and macular thickness improved by a mean of −324 μm from baseline; however, the outcomes for the overall group of 527 eyes is likely to be worse because eyes with poor outcome may be more likely to be lost to follow-up. On average, patients in our study received 12 injections, one-third achieved good VA (≥ 70 letters) and one-third poor VA (≤ 35 letters). Ongoing treatment was documented at 3 years in 31% of our cohort; however, we were able to infer cessation of therapy in 29% before 3 years.

This study improves prognostication out to 3 years for patients starting available VEGF therapy for CRVO in routine care. Current evidence derived from routine care suffers from very high rates of dropout or analyzes completers only.[14–16] Follow-up in this study was 49% at 3 years, which was far higher than comparable studies.[13] We believe that it is important to account for the outcomes of all eyes whether they were completers (49%, + 12 letters, −324 μm, 18 injections) or noncompleters (51%, + 7 letters, −288 μm, 7 injections) because there is potential for selection bias in "completers-only analyses," especially as outcomes may further deteriorate in eyes that drop out. The 18 injections at 26 visits over 3 years that we found for completers is a high-treatment burden. Better outcomes may be achieved with longer-lasting agents. Ongoing efforts to treat the causal pathology as well as the sequelae of the venous obstruction in CRVO should continue.[24,25]

Starting VA is one of the strongest predictors of outcomes first reported by the Central Vein Occlusion Study (CVOS) group, considering ischemic and nonischemic subtypes together.[26] One-quarter of our cohort had *very-poor* baseline VA < 19 letters, and in keeping with CVOS, 70% had final VA ≤ 35 letters, but with so much room for improvement (mean, + 22 letters) these eyes lifted the overall primary outcome of mean change in VA in our study. Most trials require baseline VA between 19 and 73 letters for inclusion.[4,7,9,11,18,21] A subset of eyes in our study with *trial-eligible* baseline VA (19–73 letters [68%]) had mean change in VA of + 7 letters, less than our overall cohort and the RCT extension studies, which had improvements of around + 14 letters at 3 to 4 years.[17,27] Unfortunately, outside the strict controls of RCTs, the results achieved in everyday practice are generally less, as seen with this study.

An estimation of the number of patients with CRVO who could discontinue treatment within 3 years was a major outcome of this study. We had to infer cessation from suspensions of therapy, and reasons specifically given for discontinuation, available in 102 (38%) of 270 non-completers, that were indicative of cessation. The final treatment status (ongoing or ceased) was identified in 61% of our cohort. Our estimate that an equal number of eyes were still requiring treatment after 3 years is similar to that of the RETAIN extension study.[17] Unlike the RETAIN study, we found that very few eyes (68/527 [12%]) achieved edema resolution while off treatment. We observed erosion of VA gains from a peak at 2 to 36 months. This trend may well continue if persistent oedema is inadequately treated in subsequent years.[27]

We observed a more lenient approach to the treatment of CME in this routine practice. Tolerance of CME is not in keeping with either a *pro-re-nata* or a *treat-and-extend* regime, both of which advocate treatment in the presence of active disease. Tolerance of CME was most apparent during suspensions of therapy in what seemed to be attempted withdrawal of treatment in many eyes. These periods of ≥ 6 months without treatment either continued to final review with maintenance of VA and CST, or they ended with treatment being restarted because VA and CST deteriorated unacceptably without treatment. The bimodal distribution of VA in eyes that suspended therapy hinted at either a successful conclusion or futility of further treatment.

We have previously reported superiority of aflibercept over ranibizumab at 12 months in CRVO using models predicting VA and CST response.[28] In this study, a similar

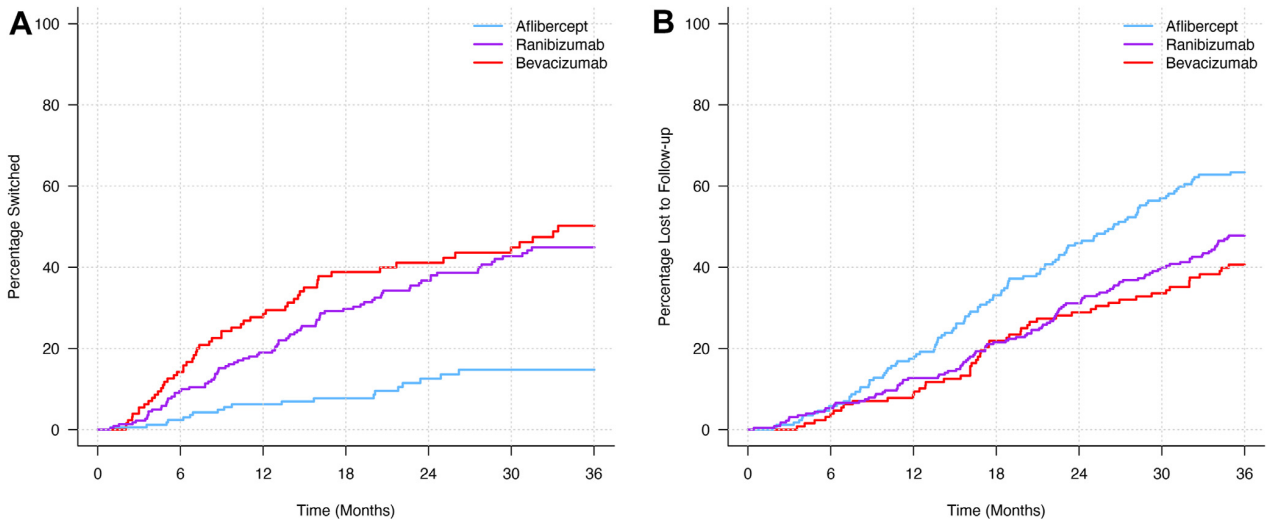

Figure 2. Kaplan–Meier survival curves describing time to (**A**) switching from the original VEGF inhibitor, and (**B**) noncompletion of 36 months by initial VEGF inhibitor.

approach that included bevacizumab was used over 36 months. We found no significant drug-based difference in predicted VA beyond the first year, similar to other 2-year comparative analyses, extending support for all 3 agents as viable treatments over 3 years.[11,12] We did, however, find that aflibercept was better at reducing macular thickness than ranibizumab throughout 36 months, whereas bevacizumab was least effective.

This study has some limitations inherent in its observational design. Even though no significant demographic differences existed in drug groups at baseline, we focused on a descriptive analysis that effectively pooled eyes treated with VEGF inhibitors, including few select eyes that received steroids for completeness. We wanted to identify, in a large cohort recruited at baseline from routine care, the ongoing need for therapy at 3 years. A simple goal, but a task made difficult because of dropout. We have data on a significant number of dropouts, albeit still a minority, but enough to make valid estimates of what the reasons were in the entire dropout cohort so that our general estimates of the requirement for ongoing treatment are likely accurate. We used models to impute outcomes in noncompleters and switchers to avoid overusing last observation carried forward. The models compared agents utilizing the entire cohort, rather than the unadjusted outcomes of monotherapy completers, which were eroded differently by switching and noncompletion. Why 1 agent was started over another is unknown but was likely based on availability, as was switching. This study complements but does not try to emulate the experimental design of RCTs—it offers a 3-year overview of outcomes in eyes that start VEGF therapy with CRVO in routine clinical care. The RVO module of the FRB! registry records only a minimum essential outcome set. It has high data finalization (95%) rates, and FRB! physicians agree to enter data on $\geq$ 85% of relevant patients when they participate, making the results of our study generalizable to a broad population.

This study illustrates the large investment in time and treatment required to achieve reasonable visual outcomes in patients with CRVO encountered in routine clinical practice. Treatment was more intensive in the first year, then tapered off in the second and third years (mean of 8, 5, and 4 injections, respectively). We did not find any difference in VA outcomes among the 3 available drugs; however, eyes treated with aflibercept had larger reductions in CST. It seemed that around half of the patients starting injections for CRVO will still need them 3 years later to maintain their vision. There was a significant noncompleter rate of 51% with the cessation of treatment linked to resolution of the occlusion seen only in a small percentage. Tolerating some disease activity without treatment may be acceptable in some patients, in others, the burden of therapy and what may be perceived as a less than satisfactory visual response cause a significant number to give up or fail to attend.

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HUMAN SUBJECTS: Human subjects were included in this study.

Ethics and data protection approval was granted in Australia and New Zealand—Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09); United Kingdom—Caldicott Guardian (Until Sept 2024); Ireland—Mater Private Hospital (IRB, 1/378/2130); Spain—Comite Etico de Investigacion Medica, Hospital Clinic de Barcelona (2015/57-OFT-HUSC); Italy—IRCCS Ca Granda Foundation Maggiore Policlinico Hospital; France—Société Française d'Ophtalmologie (2017_CLER-IRB_ll-05). Patients gave their informed consent, which was "opt-in" in European centers and "opt-out" in Australia and New Zealand, as approved by local ethics committees. Due to the noninterventional nature of the registry, the Medical Ethics Committees in Italy and the Netherlands ruled that approval was not required for this study. The study adhered to the tenets of the Declaration of Helsinki and strobe checklists for reporting observational studies.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Hunt, Nguyen, McAllister, Alforja, Barthelmes, Gillies.

Analysis and interpretation: Hunt, Nguyen, Gillies.

Data collection: Hunt, Nguyen, Bhandari, Ponsioen, McAllister, Arnold, Young, Gabrielle, Mehta, Toole, Ventura, Barthelmes, Gillies.

Obtained funding: Gillies, Barthelmes.

Overall responsibility: Hunt, Nguyen, Bhandari, Ponsioen, McAllister, Arnold, Young, Gabrielle, Mehta, Toole, Alforja, Ventura, Barthelmes, Gillies.

Abbreviations and Acronyms:
CI = confidence interval; **CME** = cystoid macular edema; **CRVO** = central retinal vein occlusion; **CST** = central subfield thickness; **FRB!** = Fight Retinal Blindness!; **RC** = randomized controlled trial; **SD** = standard deviation; **VA** = visual acuity.

Keywords:
Aflibercept, Bevacizumab, CRVO, Ranibizumab.

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Three-Year Outcomes of VEGF Inhibitors in Naive Branch Retinal Vein Occlusion

Fight Retinal Blindness!

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Purpose: To evaluate the 3-year outcomes of VEGF inhibitors in the treatment of cystoid macular edema due to branch retinal vein occlusion (BRVO) in an international multicenter cohort of eyes.

Design: Multicenter, international, BRVO database study.

Subjects: Seven hundred forty-seven patients (760 eyes) undergoing intravitreal therapy for BRVO for 3 years in a multicenter international setting.

Methods: Demographics, visual acuity (VA) in logarithm of the minimum angle of resolution letters, central subfield thickness (CST), treatments, number of injections, and visits data was collected using a validated web-based tool.

Main Outcome Measures: Visual acuity gain at 3 years in logarithm of the minimum angle of resolution letters. Secondary outcome measures included anatomical results, treatment pattern, and percentage of completers. A subgroup analysis by study drug was conducted for clinical outcomes.

Results: Mean adjusted VA change was +11 letters (95% confidence interval 9−13), mean adjusted change in CST was −176 μm (−193, −159). Median number of injections/visits was 16 of 24 at 3 years of follow-up. Most eyes received VEGF inhibitors exclusively (89%, n = 677) and as a monotherapy in 71% (n = 538). Few eyes were switched to steroids (11%, n = 83). Suspensions in treatment >180 days occurred in 26% of study eyes. Aflibercept showed greater CST reductions (−147 vs. −128 vs. −114 μm; $P < 0.001$) and significantly lower switching rates (14% vs. 38% vs. 33%; $P < 0.001$) compared with ranibizumab and bevacizumab, respectively.

Conclusions: This international study of 3-year BRVO outcomes after starting treatment with VEGF inhibitors found adequate visual and anatomical results in routine clinical care. Visual outcomes were similar among the different initiating VEGF inhibitors, although eyes starting with aflibercept had better anatomical outcomes and a lower switching rate.

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Supplemental material available at www.ophthalmologyretina.org.

Intravitreal VEGF inhibitors are the current first-line treatment option for the management of cystoid macular edema secondary to branch retinal vein occlusion (BRVO).[1,2] The efficacy of aflibercept and ranibizumab was demonstrated in randomized controlled trials (RCTs) with strict inclusion and exclusion criteria—which do not always reflect the broader population treated in routine clinical care.[3−5] There is increasing interest in clinical setting studies to address this knowledge gap as their findings are representative of the wide cohort of patients who are treated with these agents.[6−10] To date, most routine clinical care data on VEGF inhibitors for BRVO are retrospective cohorts of patients from single centers.[11,12] Invariably, the outcomes achieved in these routine clinical care data are inferior to those observed in RCTs, often due to a reduced number of injections being delivered.[9,10]

One significant limitation of existing routine clinical care data is the short duration of the follow-up and this is particularly relevant to the outcome of treatment with VEGF inhibitors which are short acting therapies requiring frequent reinjections to maintain treatment efficacy. As a consequence of the short duration of follow-up, the completion

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rate in many existing routine clinical care data is low with drop-out rates ranging from 50% up to 80% being reported. In the Luminous study (n = 326 eyes), 54% were lost to follow-up at 12 months, and in the United Kingdom Electronic Medical Records users group national report (n = 5661), the lost to follow-up rate was 80%.[13,14] These factors significantly limit the evaluation of outcomes achieved by these agents in routine clinical care, particularly when evaluating their efficacy beyond 12 months.

The Fight Retinal Blindness (FRB!) registry is an international multicenter project which consists of an audit tool for the collection of clinical data from patients receiving treatment with intravitreal therapies.[15] This platform has allowed the collection of large data sets of eyes treated with VEGF inhibitors for neovascular age-related macular degeneration, diabetic macular edema, or retinal vein occlusion (RVO).[16–18] We have recently reported the 12-month clinical outcomes achieved with VEGF inhibitor drugs, bevacizumab,[19] ranibizumab, and aflibercept.[20]

We investigated the long-term outcomes achieved with VEGF inhibitors in an international multicenter cohort of treatment-naive BRVO eyes treated and followed for up to 3 years. The treatment patterns, switching strategies, dropout rates, and possible inter-drug differences in the visual and anatomical outcomes in routine clinical care were assessed.

Methods

Study Design and Setting

This was a database observational study using the FRB! registry.[15] We analyzed the anonymized data captured from routine practice retrospectively adhering to the tenets of the Declaration of Helsinki, following the STROBE checklists for reporting observational studies and without interfering with treatment decisions made by physicians in consultation with their patients.[21] The web-based RVO module of the FRB! registry collects a prospectively defined, minimum, patient-centered outcomes set with mandatory fields populated at each clinical visit that are numeric, mutually exclusive or from a drop-down menu. No problems were identified with the data collection. Enrollment required a baseline visit (defined as the first treatment visit) that recorded the type of RVO, presence or absence of key risk factors in addition to parameters common to all subsequent visits including the logarithm of the minimum angle of resolution visual acuity (VA; best of uncorrected, corrected, or pinhole) expressed in letters, central subfield thickness (CST [μm]), assessed with OCT using the same machine for the same patient throughout, treatments given, procedures performed, and adverse events.

Ethics and data protection approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09, Australia and New Zealand), the Caldicott Guardian (Sept 2024, United Kingdom), Mater Private Hospital, Dublin (IRB, 1/378/2130, Ireland), Comité Etico de Investigación Medica, Barcelona (HCB/2018/0123, Spain), IRCCS Ca Granda Foundation Maggiore Policlinico Hospital (Italy), and Société Française d'Ophtalmologie (2017_CLER-IRB_ll-05, France). Local ethics committees approved consent as "opt-in" in European centers and "opt-out" in Australia and New Zealand. Because of the non-interventional nature of the registry, approval of the registry in the Netherlands was not needed according to the Medical Ethics Committee of the Academic Medical University Centre, the Netherlands.

Patient Selection and Definitions

We included in the analysis all treatment-naive patients with BRVO that commenced treatment with either bevacizumab (1.25 mg Avastin; Genentech, Inc/Roche), aflibercept (2 mg Eylea, Bayer) or ranibizumab (0.5 mg Lucentis, Genentech Inc/Novartis) between June 1, 2010 and June 1, 2020. Central and hemi-RVOs were excluded. Eligible patients must have had ≥3 injections. Treatment regimens were driven by local guidelines according to routine clinical care. "Completers" were defined by follow-up ≥1095 days. Treatment during the 3-year study was either "Monotherapy" (the original VEGF only), "VEGF-Switched" (≥2 alternate VEGF injections) or "Steroid-Switched" (≥1 steroid injection). "Suspension" of therapy was arbitrarily defined as observed periods without an injection for >180 days. Suspensions of therapy were not interruptions in data entry or in patient follow-up. They were periods containing visits at which no treatment was delivered—reflecting an active decision to suspend therapy.

Outcomes

The primary outcome measure was mean change in VA 36 months after the first treatment visit. Secondary outcomes included percentage of eyes with final VA ≥70, VA ≤35 letters, VA gain or loss ≥15 letters; mean change in CST; suspensions of therapy; visits and injections; noncompletion; switching and adverse events.

Statistical Analysis

Data were summarized with descriptive statistics, including counts and percentages for categorical variables; and mean, standard deviation, 95% confidence intervals, and median with first and third quartiles (Q1, Q3) for continuous variables. Observations began at the first treatment visit and continued until the 36-month visit (1095 ± 90 days). We compared VEGF agents using longitudinal models to predict VA and CST outcomes had all eyes maintained their original therapy through 36 months. The models were built using all available observations while eyes were in receipt of their original drug. Adjustments for baseline age and baseline VA (or CST) were fixed effects. Practice location and bilaterality were considered random effects. This approach was preferred over comparing select eyes that were still receiving their original drug at 36-months because switching and noncompletion had eroded the original drug groups differently.

Unadjusted outcomes were reported in all eyes and based on treatment received (monotherapy, VEGF-switched, or steroid-switched), observations were not censored after switching and last observation was carried forward in noncompleters. Outcomes in switchers at the time of switch and at final review were also reported. Kaplan–Meier survival curves were generated for switching and noncompletion with Cox-proportional hazards models comparing time to events by VEGF agents.

R version 4.2.3 (http://www.R-project.org/) was used for statistical analysis utilizing the *mgcv* (version 1.9-0) and *itsadug* (version 2.4.1) packages for generalized additive mixed effects models, the *survival* (version 3.5-7) package to generate event based outcomes, and *coxme* (version 2.2-18.1) for comparing Kaplan–Meier estimates by drug.[22]

Results

Study Participants

We identified 760 treatment naive eyes with cystoid macular edema due to BRVO that started VEGF inhibitors between June 1, 2010 and June 1, 2020 (Table 1). Baseline mean (standard

Table 1. Baseline Demographics of Patients with Branch Retinal Vein Occlusion in the Study

Eyes, n	760
Patients, n	747
Initial VEGF inhibitor	
Bevacizumab, n (%)	252 (33%)
Ranibizumab, n (%)	273 (36%)
Aflibercept, n (%)	235 (31%)
Female, % patients	53%
Age, mean (SD)	71 (11)
Baseline VA, mean (SD) letters	57 (18)
≥70 letters, %	30%
≤35 letters, %	13%
Baseline CST, mean (SD), μm	479 (162)
Hypertension, %	66%
Glaucoma, %	7%
Pseudophakia, %	19%

CST = central subfield thickness; SD = standard deviation; VA = visual acuity.

deviation) age was 71 years (11), mean VA was 57 letters (18), and mean CST was 479 μm (162) overall. Demographics were broadly similar between groups whether stratified by initial VEGF inhibitor or by the treatment they received >3 years (Tables S2, S3, available at www.ophthalmologyretina.org).

Visual and Anatomical Outcomes

In all eyes, 36-month crude mean change (95% confidence interval) in VA was +11 letters (10, 12) and CST was −169 μm (−182, −156). Mean final VA (standard deviation) was 68 (18) letters, 41% of eyes gained and 7% lost ≥15 letters; 63% had VA ≥70 letters; and 7% had VA ≤35 letters (Table 4). Response to VEGF inhibitors combined was plotted in Figure 1 (censoring only after steroids). We used models to compare response to each VEGF inhibitor (censoring after any switch) and found no difference in adjusted change in VA despite a significantly greater adjusted mean change in CST with aflibercept monotherapy (−147 μm), over ranibizumab monotherapy (−128 μm), and bevacizumab monotherapy (−114 μm; $P < 0.01$; Fig 2). Clinical outcomes specifically for eyes starting with good (≥70 letters) and poor (≤35 letters) initial VA are presented in Table S5 (available at www.ophthalmologyretina.org).

Treatments, Visits, and Suspensions of Therapy

The majority of eyes only had VEGF inhibitors (677 [89%]), mostly their original agent (538 [71%]), or an alternate VEGF inhibitor (139 [18%]). Few eyes switched to steroids (83 [11%]; 10 triamcinolone, 73 dexamethasone implant). The entire cohort received a median (Q1, Q3) of 11 (6, 19) injections, at 19 (12, 26) visits during the 36-month study. The completers (416/760 [55%]) had a median of 16 (9, 22) injections at 24 visits (Table 4). The mean number of injections of any agent given in the first, second, and third year was 7.7, 4.7, and 4.1 in eyes that completed each of those years respectively. Other treatments included sectoral photocoagulation delivered in 136 of 760 (18%) eyes, unrelated to the total number of VEGF injections given in 3 years (median, 13 injections), but more often in eyes switched to steroids than eyes not switched to steroids (29% vs. 18%; $P = 0.01$); and focal laser delivered in 78 of 760 (10%) eyes that achieved a mean final VA of 71 letters, but these eyes required more injections than the wider cohort (23 vs. 12 injections; $P < 0.01$). Posterior segment neovascularization occurred in 18 patients that received fewer injections than average (8 vs. 11 injections; $P = 0.04$), were treated with sectoral photocoagulation and had mean final VA of 73 letters.

Suspensions of therapy lasting >180 days during the 3-year study occurred at least once in 331 of 760 (44%) eyes. In 198 eyes (26%), the suspension continued to final review, a mean of 18 months later with mean change in VA of +11 letters from baseline. In contrast, 176 eyes (23%) had a temporary suspension; they restarted therapy within 36 months, only to achieve mean change in VA of +7 letters at final review. We cannot accurately infer cessation of treatment in eyes that maintained suspension of therapy through final review but when combined with eyes that had discontinuation reasons suggesting cessation (9%, below), it was a group of similar size to those still requiring treatment (39%) at 3 years.

Noncompletion of 36 Months

Outcomes in noncompleters (289 [47%]) at final review were very similar to those of 36-month completers including the primary outcome of mean change in VA (95% confidence interval) +11 letters (9, 13), mean final VA 68 letters, and mean CST 311 μm (Table S6, available at www.ophthalmologyretina.org). Noncompletion rates differed significantly based on initial VEGF inhibitor (bevacizumab 44%, ranibizumab 41%, and aflibercept 63%; $P < 0.001$; Fig 3A). The 63% of aflibercept eyes that noncompleted did so with good outcomes at final review to suggest many may have concluded therapy including mean change in VA of +12 letters, mean VA of 70 letters, and mean CST 285 μm. Discontinuation reasons in all eyes were available in 68 of 344 (20%) noncompleters, 15 transferred to another physician; cessation was implied (53 eyes) in 18 that had "treatment successful," 11 "declined treatment," 2 had "medical contraindications," and in 5 "further treatment was futile," and 17 patients died.

Switching

Switching occurred in 222 of 760 eyes (29%). Switching rates differed significantly based on initial VEGF inhibitor (bevacizumab 33%, ranibizumab 38%, and aflibercept 14%; $P < 0.001$; Fig 3B). More than half of all switching was to aflibercept (121/760 [16%]). Aflibercept was the last injection given in 323 of 760 eyes (42%). Steroid switching was to the dexamethasone implant (73/760 [10%]) or triamcinolone (10/760 [1%]). Eyes that switched to an alternate VEGF therapy (139/760 [18%]) had similar outcomes to nonswitchers (Table 4) but received more injections (18 vs. 10; $P < 0.01$) and completed 3 years more often (72% vs. 55%; $P < 0.01$). Eyes that switched to steroid (83 [11%]) lost around 4 letters on average from baseline, had more cataract surgery (39% vs. 11%; $P < 0.01$) and more often started new therapy to control intraocular pressure (13% vs. 2%; $P < 0.01$) than eyes that did not receive steroids. New macular

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Table 4. Three-Year Outcomes in All Eyes and Based on Treatment Received

	All Eyes	Monotherapy	VEGF-Switched	Steroid-Switched
Eyes, n (% entire cohort)	760 (100%)	538 (71%)	139 (18%)	83 (11%)
VA baseline, mean (SD)	57 (18)	57 (18)	57 (19)	59 (15)
VA final, mean (SD)	68 (18)	70 (17)	68 (18)	55 (24)
VA change, mean (95% CI)	11 (10–12)	13 (12–15)	11 (8–15)	−4 (−10 to 2)
Gain ≥15 letters, %	41%	44%	41%	19%
Loss ≥15 letters, %	7%	4%	6%	28%
VA ≥70, %baseline/%final	30%/63%	30%/67%	32%/60%	28%/39%
VA ≤35, %baseline/%final	13%/7%	14%/5%	14%/6%	8%/18%
CST baseline, mean (SD)	479 (162)	479 (162)	473 (151)	494 (179)
CST final, mean (SD)	311 (110)	295 (90)	331 (113)	384 (175)
CST change, mean (95% CI)	−169 (−182 to −156)	−184 (−199 to −169)	−142 (−173 to −111)	−110 (−157 to −62)
Injections, median (Q1, Q3)	11 (6, 19)	10 (6, 17)	18 (11, 25)	11 (7, 15)
Visits, median (Q1, Q3)	19 (12, 26)	16 (10, 23)	25 (18, 32)	25 (20, 30)
Suspension at final review, n (% column)*	198 (26%)	149 (28%)	28 (20%)	21 (25%)
Focal laser treatment, n (% column)	78 (10%)	49 (9%)	18 (13%)	11 (13%)
Sectoral photocoagulation, n (% column)	136 (18%)	76 (14%)	34 (24%)	26 (31%)
Elevated IOP requiring treatment, n (% column)	25 (3%)	8 (1%)	6 (4%)	11 (13%)
Cataract surgery performed, n (% column)	84 (11%)	43 (8%)	9 (6%)	32 (39%)
36-mo completers, n (% column)	416 (55%)	256 (48%)	100 (72%)	60 (72%)
VA change in completers, mean (95% CI)	11 (9–13)	13 (11–16)	14 (9–18)	−3 (−9 to 4)
CST change in completers, mean (95% CI)	−176 (−193 to −159)	−192 (−213 to −170)	−156 (−190 to −122)	−138 (−184 to −93)
Injections in completers, median (Q1, Q3)	16 (9, 22)	15 (9, 21)	22 (14, 28)	10 (7, 15)
Visits in completers, median (Q1, Q3)	24 (19, 30)	23 (17, 29)	27 (22, 34)	26 (22, 32)

All eyes – outcomes without censoring observations after switching and using last observation carried forward in noncompleters; monotherapy – eyes treated with initial VEGF inhibitor only; VEGF-switched – ≥2 alternate VEGF injections; steroid-switched – ≥1 steroid injection (10 eyes – triamcinolone, 73 eyes – dexamethasone implant).
CI = confidence interval; CST = central subfield thickness; IOP = intraocular pressure; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; VA = visual acuity.
*No treatment observed for >180 days leading up to and including 36-months or final review in noncompleters.

changes were recorded more frequently in eyes that switched, including epiretinal membrane, macular hole, pigment change, or atrophy (41/538 [8%] monotherapy eyes, 24/139 [17%] alternate VEGF eyes, and 24/83 [29%] steroid eyes; $P < 0.01$). Specific switching outcomes at time of switch and final review are described in Table S7 (available at www.ophthalmologyretina.org).

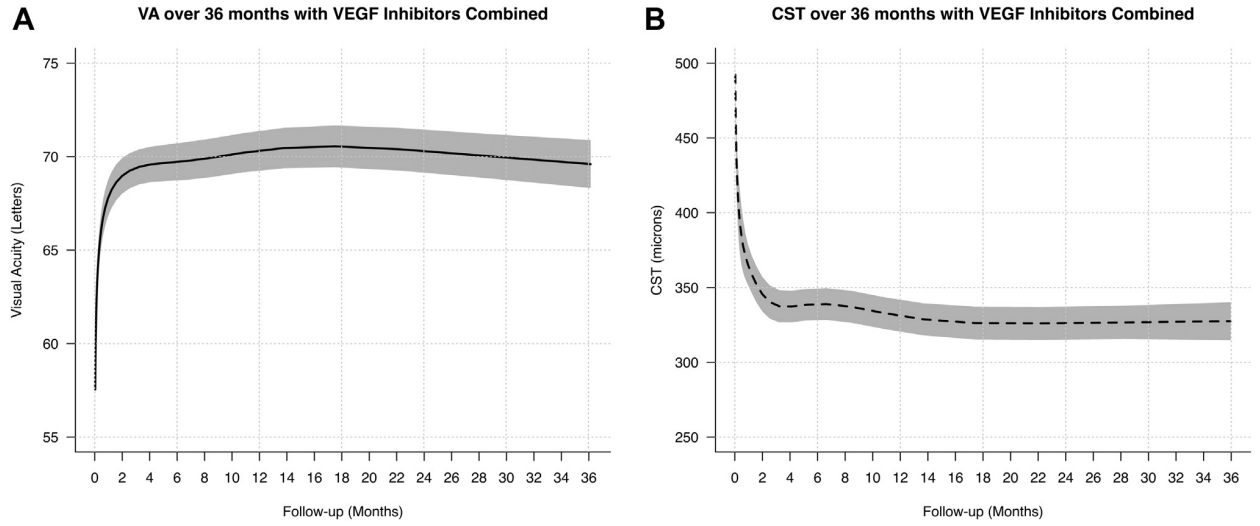

Figure 1. Mean VA (**A**) and CST (**B**) with VEGF inhibitors combined. Observations from all eyes while receiving VEGF inhibitors only (original or alternate, observations after receipt of any steroid were censored). The plot is smoothed with the mean surrounded by 95% confidence intervals (1.96 × standard error). CST = central subfield thickness; VA = visual acuity.

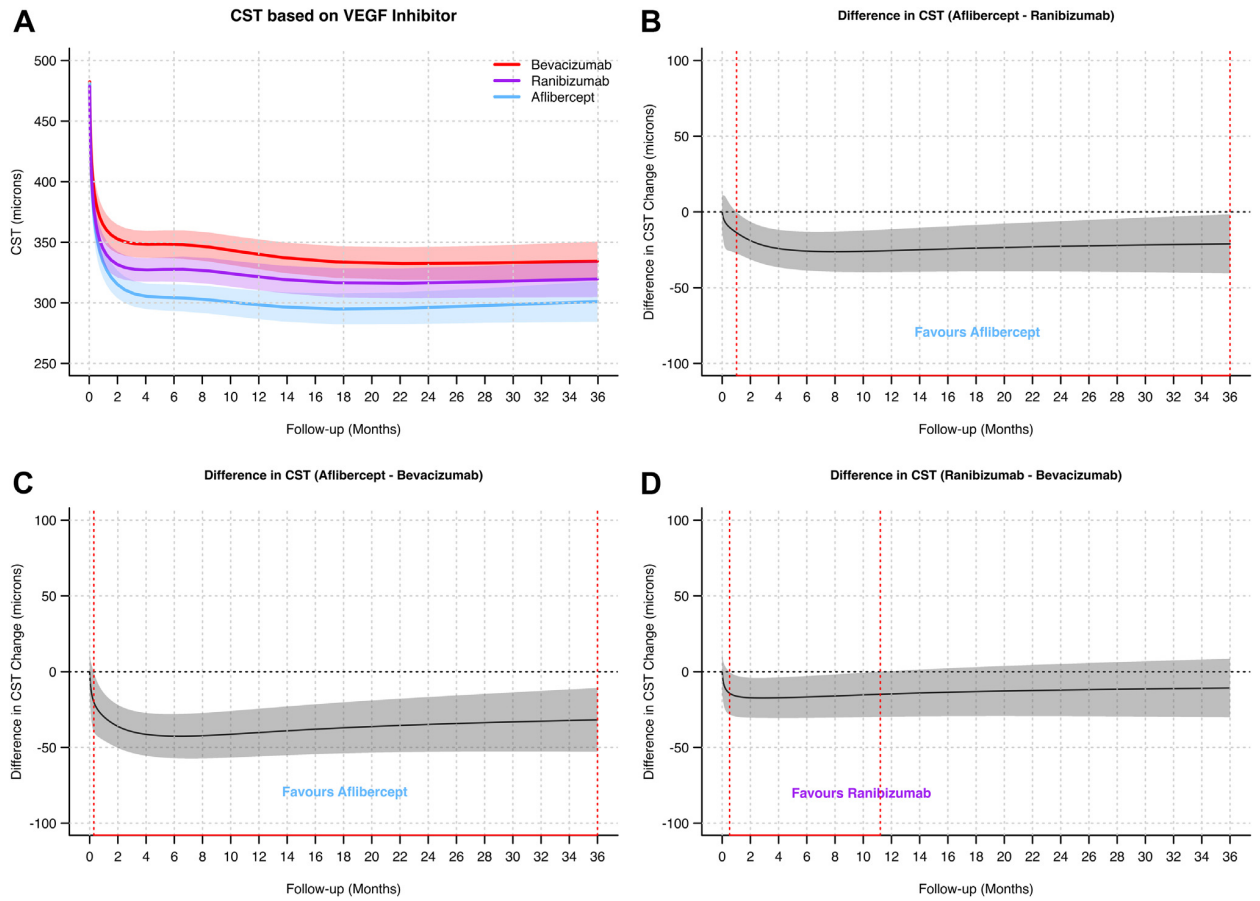

Figure 2. Mean CST by VEGF inhibitor over 3 years. Significant drug-based differences in predicted CST in panel **A** occurred throughout 36 months. Subtracting predictions, with 95% confidence intervals (CIs; 1.96 × standard error) included in panels **B** to **D**, are in favor of aflibercept over ranibizumab over bevacizumab (*dashed red lines* indicate periods of significant difference when CIs are not overlapping). CST = central subfield thickness.

Adverse Outcomes

A total of 10 142 injections were delivered in the study with 3 vitreous hemorrhages (mean final VA, 75 letters), 1 traumatic cataract (65 letters), and 1 case of infectious endophthalmitis (30 letters).

Discussion

This study describes an overall visual gain of +11 letters at 3 years with a median number of 16 injections and 24 visits in a multicenter international cohort of treatment naive BRVO eyes treated in routine clinical care. The data described in this report extend the preliminary findings described in our previous 12 months outcomes analysis,[19,20] with marked visual gains during the loading dose maintained in the extension phase beyond the first year of treatment. The subgroup analysis by treatment drug is consistent with our previous findings, which revealed greater anatomical results for aflibercept compared with other compounds but no differences in visual outcomes. Additional findings are the treatment patterns observed favoring VEGF inhibitor monotherapy and the similar results observed in completers and noncompleters, suggesting that the reasons for dropout in many eyes were likely because of disease resolution rather than lack of clinical response to VEGF inhibitors.

The visual results observed in this study are inferior to previous RCTs and consistent with previous routine clinical care data with shorter follow-up.[10] We observed an overall VA gain of +11 letters at 3 years, which was observed with the loading dose and maintained thereafter, consistent with our previously reported 12 month data.[20] Interestingly, we report a relatively high number of injections, which may have avoided the risk of undertreatment frequently reported by routine clinical care data. However, this 3-year gain is still lower than the BRAVO and HORIZON extension study results at 2 years (+17.5 letters) and VIBRANT at 1 year (+17.1 letters).[3,4,23] The observed inferior gains in mean VA could be explained in part by the higher baseline mean VA of our study cohort (57 letters vs. 53 letters) and our thinner mean CST (479 vs. 551 μm) compared with BRAVO. Our cohort's baseline characteristics were similar to VIBRANT (58.6 letters and 558 μm).[3,4] These results,

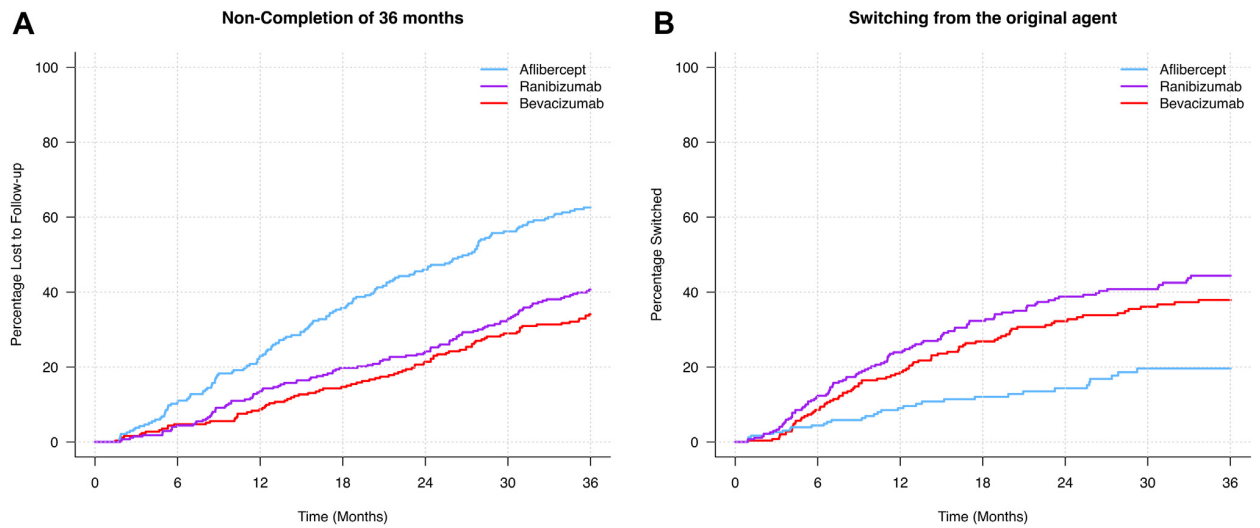

Figure 3. Percentage of eyes lost to follow up (**A**) and percentage of eyes switched from the original agent (**B**) during follow up.

however, are consistent with a recent Cochrane review that also pointed out that in BRVO the main visual gains with VEGF inhibitors were achieved at 6 months and then maintained at 12 months.[7] Very few RCT and routine clinical care data studies have explored these outcomes beyond 1 year, the few that have reported 24 month outcomes had a very reduced number of eyes.[8,24–28] In this report, we demonstrate that VEGF inhibitors are able to maintain these gains up to 3 years in routine clinical care.

One of the main objectives of our study was to provide specific details on how BRVO was managed over 3 years. We found a median number of 16/24 injections/visits over 3 years in completers. We report a higher number of injections compared with the RETAIN study (n = 12.9 injections/3 years)[24] and other routine clinical care data (5.9 and 6.8 injections/3 years), which could explain the positive results we found.[8,29] Suspensions of therapy for 180 days during the 3-year study were observed in approximately half of the study cohort (44%, 331/760), and were sustained at the end of the follow-up in a quarter of these cases (26%, 198/760) with good outcomes (+11 letters, 63% >70 letters). Relapses after a suspension were observed in approximately a quarter of the study eyes (176/760, 23%) with lower VA gain (+7 letters). A third of the cases were still receiving treatment at 3 years (296/760, 39%).

Most eyes studied received treatment exclusively with VEGF inhibitors (89%, n = 677), including 71% that received monotherapy using the same agent throughout. Switching to a different VEGF inhibitor was found in 18% of eyes, most (84%) that switched did so to aflibercept, probably related to the greater anatomical response observed with this agent in our series. Very few eyes were switched to alternative therapies such as steroids (10%, n = 83). This is relevant, as the switch to steroids frequently occurs early in the course of the disease[30] with very limited long-term data. The 136 (18%) eyes that received sectoral panretinal photocoagulation received a similar number of injections as the overall cohort, suggesting that it does not exacerbate cystoid macular edema in eyes receiving intravitreal therapy for BRVO.

The 3-year visual and anatomic outcomes of completers were very similar to noncompleters, suggesting that some eyes may have discontinued treatment successfully. This is different from other conditions such as neovascular age-related macular degeneration, where eyes that discontinue treatment commonly have worse outcomes. This may be explained by the different pathophysiology of the 3 conditions. As described in the original BVOS study, in some eyes with RVO the event may be self-limiting and may be reperfused with collateral vessels,[31] whereas age-related macular degeneration is a chronic condition. Similar to our report on 12-month BRVO outcomes, eyes starting with aflibercept achieved better anatomic outcomes through 36 months, even though VA gains were not significantly different between the agents. This may be explained again by the pathophysiology of BRVO, which predominantly affects the inner retinal layers and spares the outer retina, preserving the ability to maintain good levels of VA even in eyes with an incomplete anatomical response.

This study has some limitations, beyond its observational design. We excluded hemiretinal vein occlusions, that have larger improvements in VA with VEGF inhibitors than BRVO in routine care,[32] unlike many of the previous RCTs such as BRAVO, VIBRANT, or BRIGHTER which enrolled such patients. This is potentially another reason why our clinical setting results are inferior to RCTs.[4,23,33] The treatment regimens were not homogeneous between centers, as is inevitable in a multicenter international case series where local policies are often directed by national regulatory bodies (i.e., drug agencies, national society's recommendations, etc.) and individual practitioners may have their own unique approach. This is not necessarily a limitation as it reflects routine clinical care practice.[18] We do not have full 3-year outcome data on approximately half the cohort; however, the good final outcomes of non-completers suggest that many may have discontinued

therapy successfully. Finally, the participating centers contributing data to the FRB! project may not reflect all practices, as its use represents the implementation of a measure of the quality of care.

In conclusion, this report describes the 3-year visual and anatomical outcomes achieved with VEGF inhibitors in a large international multicenter study of eyes treated in routine clinical care, using a validated web-based registry for data collection. Our findings extend our published 12-month clinical setting outcomes for BRVO, with the initial visual gains generally maintained for up to 3 years of follow-up. At least half of the eyes were still requiring treatment but a significant number had been able to discontinue treatment with good vision.

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Footnotes and Disclosures

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No animal subjects were used in this study.

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Obtained funding: Barthelmes, Gillies, Zarranz-Ventura

Overall responsibility: Hunt, Barthelmes, Gillies, Zarranz-Ventura

Abbreviations and Acronyms:
BRVO = branch retinal vein occlusion; **CST** = central subfield thickness; **FRB** = Fight Retinal Blindness; **RCT** = randomized controlled trial; **RVO** = retinal vein occlusion; **VA** = visual acuity.

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Aflibercept, Branch retinal vein occlusion, Fight Retinal Blindness, Ranibizumab, VEGF inhibitors.

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APPENDIX V: Related Publications

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ORIGINAL ARTICLE-CLINICAL SCIENCE

Clinical & Experimental Ophthalmology WILEY

Impact of cataract surgery on patients receiving intravitreal therapy for retinal vein occlusion

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Abstract

Background: To assess clinical outcomes of cataract surgery in eyes treated with intravitreal injections for cystoid macular oedema (CMO) secondary to retinal vein occlusions (RVOs).

Methods: Eyes receiving intravitreal injections for CMO secondary to RVOs that underwent cataract extraction were identified from the Fight Retinal Blindness! Registry and matched 1:1 by 9 parameters with phakic controls also receiving intravitreal injections for the same condition. VA change at 12 months, central subfield thickness (CST) and injection frequency before and after surgery were compared between the two groups. The effect of baseline features on the final VA including age, CST, treatment frequency among others was tested.

Results: We included 193 eyes that had cataract extraction (exposed) matched with 193 phakic eyes that did not have surgery (matched). VA (95%CI) changed by +9.9 (7, 12.8) letters in exposed eyes versus −2.4 (−4.1, −0.7) letters in matched eyes ($p < 0.01$). The mean [SD] VA at 12 months was similar in exposed and matched eyes [60.7 (23.0) vs. 61.1 (24.3) letters, respectively,

$p = 0.81$]. The mean [SD] CST was similar between groups before and at surgery, but it was greater in exposed compared with matched eyes [353 (152) vs. 322 (123) μm, respectively, $p = 0.03$] 12 months after surgery. Exposed eyes received more injections [median (range)] than matched eyes during the 12 months after surgery [5 (3, 7) vs. 4 (1, 6), injections, $p < 0.01$].

Conclusions: Cataract extraction delivered good visual outcomes in patients treated for CMO secondary to RVOs. More injections were required on average in the 12 months after surgery in eyes undergoing surgery compared to matched controls.

KEYWORDS

anti-VEGF, cataract surgery, outcomes, retinal vein occlusions, RVO

1 | INTRODUCTION

Retinal vein occlusions (RVOs) are the second commonest retinal vasculopathies affecting predominantly white populations, with an incidence per year ranging from 0.03% to 0.12%.[1,2] Approximately 16 million people are estimated to be affected by this condition worldwide.[3]

Patients with RVOs often develop macular edema, managed with intravitreal injections of either anti-vascular endothelial growth factor (VEGF)[4] or steroids.[5,6] To collect real-life data of anatomical and functional outcomes, a dedicated RVO module has been developed by the Fight Retinal Blindness! (FRB!) project that is now widely used in routine clinical practice. The registry uniquely collects a prospectively defined treatment-outcomes dataset regarding care delivered in routine practice. To ensure data integrity, visits can only be finalised when mandatory fields are 100% complete and within range (Supporting Information).[7]

As increasing age is a major risk factor for RVO,[8] a substantial number of RVO patients also have cataract that requires surgical extraction. Cataract surgery is highly effective,[9] but in patients being treated for RVO there is a fear that surgically induced inflammation worsens existing cystoid macular oedema (CMO).[10]

Previous studies on a relatively limited number of patients have reported a higher incidence of post-surgical CMO[11] or a worsening in previously treated CMO[12] in eyes with RVO undergoing cataract surgery. On the other hand, a larger multicenter real-world study recently reported a significant improvement in postoperative vision after cataract surgery in eyes with RVO but without focusing on those already trated for CMO.[13] In this scenario, the real impact of cataract surgery on visual acuity, CMO and rate of intravitreal injections in eyes with RVO is still unclear with many clinicians still in doubt to either pursue or defer surgery in these patients.

The main purpose of this study was to evaluate outcomes 12-months after cataract removal from eyes receiving intravitreal therapy for RVO. We aimed to quantify the impact of surgery on visual acuity (VA) and macular thickness by comparing outcomes with a matched cohort not exposed to cataract surgery. We also aimed to compare injection frequency in the 12 months before and after surgery and explore factors that predicted better VA gains after cataract surgery in eyes being treated for RVO.

2 | METHODS

2.1 | Study design and setting

Data were recorded during routine clinical practice and entered the FRB! RVO module which forms part of the Save Sight Registries (SSR). This study included patients from Australia, France, Ireland, Italy, Netherlands, New Zealand, Slovakia, Spain, Switzerland, and the United Kingdom. Institutional ethics approval was obtained from the Human Research Ethics Committees of the University of Sydney, the Royal Australian and New Zealand College of Ophthalmologists, the French Institutional Review Board (IRB) (Société Française d'Ophtalmologie IRB), the Mater Private Hospital IRB, the Area 1 Milan Ethical Committee, Singhealth Singapore, Etická komisia UN-Nemocnica svätého Michala, Slovakia, the Spanish IRB (Comité Etico de Investigación Medica, Hospital Clínic de Barcelona, Spain), the Cantonal Ethics Committee Zurich, and the Caldicott Guardian at the Royal Free London NHS Foundation Trust. Approval of the use of the registry in the Netherlands was not needed according to the Medical Ethics Committee of the Academic Medical Ethics Committee of the Academic Medical University Centre due to its non-interventional nature. This study adhered to the tenets of the Declaration of Helsinki.

2.2 | Data sources/measurements

Previous treatments, lens status, hypertension, RVO type [central (CRVO), hemi-retinal (HRVO), or branch (BRVO)] and patient demographics were recorded at the baseline (first treatment) visit. The number of letters read on a LogMAR VA chart (best among corrected, uncorrected or pinhole), central subfield thickness (CST), the activity of the CMO as graded by the treating practitioner, ocular adverse events, and additional procedures including cataract surgery were recorded at each visit.

Treatment decisions including the choice and timing of treatment were at the discretion of the treating practitioner in consultation with the patient, reflecting routine clinical practice. The investigators did not intervene at any point during the study.

2.3 | Study population and groups

Phakic eyes that initiated intravitreal treatment for CMO due to RVO between 1st January 2010 and 1st June 2022 were eligible for the analysis. The cataract cohort included eligible eyes who underwent cataract surgery with at least one recorded visit 12 months (±60 days) before and after the surgery. Data on cataract grading and surgical technique are not tracked in the FRB! Registry thus they were not included in the study. The eyes exposed to cataract surgery were compared with a matched cohort of phakic unoperated eyes to assess the impact of cataract surgery on outcomes of RVO treatment. Matches met the eligibility criteria but an index visit was chosen in place of cataract surgery at a similar stage of treatment. At that index visit the matched eye must also have received similar treatment number with a similar number of injections of VEGF inhibitors and/or steroids considered separately. This was deemed necessary to ensure matches were similar to the cataract cohort that may have received steroids more often. Parameters for Mahalanobis matching included details of treatment delivered and baseline parameters [Days until cataract surgery (±90 days); initial injection type (bevacizumab, ranibizumab, aflibercept, triamcinolone, dexamethasone implant); RVO type (BRVO or CRVO {HRVO excluded}); number of injections before cataract surgery (VEGF inhibitors, Steroids counted separately); baseline age, VA, CST and hypertension].

2.4 | Outcome measures

The primary outcome was the 12-month change in VA after cataract surgery. Secondary outcomes included: 12-month change in CST; 12-month frequency of injections (compared with the preceding 12 months); 12-month percentage with VA ≥70 letters or ≤35 letters and percentage gaining or losing ≥15 letters. We analysed factors at the time of cataract surgery that were predictive of visual outcome 12 months later. VA and CST were analysed at baseline for matching, 12 months before surgery, at cataract surgery and 12 months after surgery. We plotted these to describe changes as cataract developed and outcomes of surgery in eyes undergoing treatment of RVO.

2.5 | Statistical analysis and definitions

Descriptive statistics were summarised using the mean, standard deviation (SD), median, first and third quartiles (Q1, Q3) and percentages. Continuous variables were compared using *t*-tests or Wilcoxon signed rank tests were appropriate, while categorical variables were compared using McNemar's test. We used ordinal regression to identify predictive factors of achieving VA gains 12 months after surgery of ≥15 letters, 1–14 letters or ≤0 letters. The predictive factors included patient characteristics (RVO type, age, gender, hypertension); details of the RVO treatment before cataract surgery (duration, VEGF injections, steroid, laser, adverse outcomes); and clinical parameters at cataract surgery (VA, CST, treatment interval, CMO activity). The adverse outcomes of interest included 'Neovascularisation' either in the posterior or anterior segment, and 'New macular changes affecting vision' including pigmentary changes, epiretinal membrane or macular hole. All analyses were conducted using R version 4.3.1 with the MatchIt package (V 4.5.5) for identifying matched controls and the ordinal package (V 11.16) for ordered regression analysis.[14–16]

3 | RESULTS

We included 193 eyes from 190 patients with RVO that had cataract surgery with 12 months of follow-up before and after the surgery (operated). These eyes were matched with 193 phakic eyes that did not have cataract surgery (matched). Characteristics at initial intravitreal therapy are summarised in Table 1. Matching by nine parameters produced similar operated and matched groups, including baseline mean (SD) VA [52.6 (21.2) vs. 51.3 (21.3) letters, $p = 0.56$] and CST [551 (211) vs. 553 (213) μm, $p = 0.92$]. There was exact matching by type of RVO [BRVO 109 eyes (57%); CRVO 84 eyes (43%)]. Most operated and matched eyes began intravitreal therapy with VEGF inhibitors (89% vs. 91%,

TABLE 1 Characteristics of eyes exposed to cataract surgery and matched eyes at first intravitreal treatment.

	Operated	Matched	*p* Value
Eyes	193	193	
Patients	190	192	
Gender, % female patients	54%	53%	0.92
Age, mean (SD)	70.4 (9.6)	69.8 (9.9)	0.53
RVO type, *n* (%)			
BRVO	109 (57%)	109 (57%)	1.00[a]
CRVO	84 (43%)	84 (43%)	1.00[a]
VA, mean (SD)	52.6 (21.2)	51.3 (21.3)	0.56
≤35 letters, *n* (%)	42 (22%)	39 (20%)	0.80
≥70 letters, *n* (%)	50 (26%)	38 (20%)	0.18
CST, mean μm (SD)	551 (211)	553 (213)	0.92
Initial injection, *n* (%)			
VEGF inhibitors	171 (89%)	175 (91%)	0.62
Steroids	22 (11%)	18 (9%)	

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CST, central subfield thickness; RVO, retinal vein occlusion; SD, standard deviation; VA, visual acuity.
[a]Exact matching performed on variable.

respectively, $p = 0.62$) rather than steroids (11% vs. 9%, respectively, $p = 0.62$). The agents utilised included bevacizumab (31%), ranibizumab (38%), aflibercept (21%), triamcinolone (1%) or dexamethasone implant (9%) as initial therapy.

3.1 | Outcomes 12 months before and after surgery

Visual and anatomical outcomes are summarised in Table 2 and Figure 1. Cataract surgery occurred at a median (Q1, Q3) of 879 (545, 1254) days after initial treatment in operated eyes with a matching visit in control eyes at 881 (546, 1239) days ($p = 0.52$). The primary outcome of mean change in VA (95% CI) 12 months after cataract surgery was significantly greater in operated eyes [+9.9 (7, 12.8)] letters than in matched eyes [−2.4 (−4.1, −0.7)] ($p < 0.01$). The mean VA in operated eyes was similar to matched eyes 12 months after surgery (60.7 [23.0] vs. 61.1 [24.3] letters, respectively, $p = 0.81$) despite significantly lower mean VA in the operated eyes compared with matched eyes 12 months before (57.6 [20.9] vs. 62.5 [22] letters, respectively, $p < 0.01$) and at cataract surgery (50.8 [24.2] vs. 63.5 [21.2] letters, respectively, $p < 0.01$). Significantly more operated eyes gained ≥15 letters after surgery than matched eyes [65 (34%) vs. 6 (3%)] ($p < 0.01$).

The mean CST was similar in both groups before and at cataract surgery (Table 2), with similar mean change in CST (95% CI) 12 months after surgery (+17 [−8, 42] vs. −3 [−25, 18], $p = 0.22$), but mean CST (SD) 12 months after surgery was slightly greater in operated compared with matched eyes [353 μm (152) vs. 322 (123), respectively, $p = 0.03$].

Figure 2 describes the LOESS (locally weighted scatterplot smoothing) of VA and CST after surgery through 12 months in eyes that had cataract surgery and the matched cohort. The regression predicted mean VA in the operated eyes equalised with matched eyes 112 days after surgery and remained stable through 12 months. The mean predicted CST in the operated eyes at 1, 2 and 3 months after surgery increased by 30, 36 and 37 microns on average and remained 22 microns above the preoperative level 12 months after surgery.

Fewer injections [median (Q1, Q3)] were given to operated eyes 12 months before surgery than matched eyes [5 (3, 7) vs. 6 (4, 8), injections, $p < 0.01$], but operated eyes received more frequent injections than matched eyes during the 12 months after surgery [5 (3, 7) vs. 4 (1, 6), injections, $p < 0.01$]. A higher proportion of operated eyes received steroids in the 12 months after surgery than matched phakic eyes [17 (9%) vs. 4 (2%), $p < 0.01$]. Visual and anatomical outcomes between eyes exposed to cataract surgery and matched eyes stratified by RVO type (Supporting Information).

3.2 | Predictive factors for visual acuity change after cataract surgery

In eyes exposed to cataract surgery, the VA change 12 months after surgery was categorised in order of improvement: ≥15 letters in 41/123 eyes (33%), 1–14 letters in 57/123 eyes (46%) or ≤0 letters in 25/123 eyes (20%). The ordinal regression model found that eyes with BRVO (rather than CRVO) and lower VA at time of surgery were significantly more likely to gain VA (Table 3). We found VA change after surgery was not predicted by age, CST, history of hypertension, duration of RVO treatment prior to cataract surgery, including the number of injections or type (VEGF ± steroids), immediate preoperative treatment interval, CMO activity immediately prior surgery, prior neovascular complications or macular changes affecting vision or treatment with laser.

4 | DISCUSSION

In this study using real-world data, we found cataract surgery delivered good visual outcomes in eyes with RVO.

TABLE 2 Visual and anatomical outcomes 12 months prior to cataract surgery, at cataract surgery, and 12 months after cataract surgery between operated and matched eyes. In addition to primary and secondary outcomes are descriptive data regarding outcomes 12 months prior to cataract surgery, at cataract surgery, and 12 months after cataract surgery.

	Operated	Matched	*p* Value
Primary and secondary outcomes			
Δ VA 12 m after surgery, mean (95% CI)	9.9 (7, 12.8)	−2.4 (−4.1, −0.7)	**<0.01**
VA gain ≥15 letters 12 m after surgery, *n* (%)	65 (34%)	6 (3%)	**<0.01**
VA loss ≥15 letters 12 m after surgery, *n* (%)	14 (7%)	22 (11%)	0.24
VA ≤35 letters (% 12 m before/12 m after surgery)	17%/14%	12%/16%	0.76[a]
VA ≥70 letters (% 12 m before/12 m after surgery)	37%/49%	50%/51%	0.73[a]
Δ CST after surgery, mean (95% CI)	17 (−8, 42)	−4 (−25, 18)	0.22
Total injections, 12 m before surgery, median (Q1, Q3)	5 (3, 7)	6 (4, 8)	**<0.01**
Total injections, 12 m after surgery, median (Q1, Q3)	5 (3, 7)	4 (1, 6)	**<0.01**
12 m before cataract surgery			
VA, mean (SD)	57.6 (20.9)	62.5 (22)	**<0.01**
CST, mean (SD)	371 (169)	374 (162)	0.82
At cataract surgery			
Days after first treatment, median (Q1, Q3)	879 (545, 1254)	881 (546, 1239)	0.52
VA, mean (SD), letters	50.8 (24.2)	63.5 (21.2)	**<0.01**
CST, mean (SD), μm	336 (144)	325 (145)	0.48
New macular changes before surgery, *n* (%)	36 (19%)	31 (16%)	0.59
Neovascular complications before surgery, *n* (%)	17 (9%)	10 (5%)	0.23
PRP/sectoral laser before surgery, *n* (%)	54 (28%)	44 (23%)	0.29
Focal laser before surgery, *n* (%)	22 (11%)	19 (10%)	0.74
Intravitreal steroid use before surgery, *n* (%)	62 (32%)	56 (29%)	0.58
12 m after cataract surgery			
VA, mean (SD)	60.7 (23)	61.1 (24.3)	0.81
CST, mean (SD)	353 (152)	322 (123)	**0.03**
New macular changes after surgery, *n* (%)	6 (3%)	4 (2%)	0.75
Neovascular complications after surgery, *n* (%)	3 (2%)	2 (1%)	1.00
PRP/sectoral laser after surgery, *n* (%)	9 (5%)	6 (3%)	0.60
Focal laser after surgery, *n* (%)	3 (2%)	4 (2%)	1.00
Intravitreal steroid use after surgery, *n* (%)	17 (9%)	4 (2%)	**<0.01**

Note: Bold indicate statistically significant values.

Abbreviations: 12 m, 12 months; BRVO, branch retinal vein occlusion; CI, confidence interval; CRVO, central retinal vein occlusion; CST, central subfield thickness; neovascular complications, any posterior or anterior segment neovascularisation during the study; new macular changes, pigmentary changes, epiretinal membrane or macular hole noted during the relevant time period of the study; PRP, panretinal photocoagulation; RVO, retinal vein occlusion; SD, standard deviation; VA, visual acuity; Δ, change.

[a]*p* Value comparing percentages 12 months after surgery.

VA deteriorated in eyes in our cohort as cataract developed, but 1 year after surgery it was similar to that of matched eyes that did not need cataract extraction. The only small but significant difference was the need for more intravitreal injections in operated eyes in the 12 months following the procedure compared to matched eyes.

The patients included in this study were a unique subset with almost a third receiving steroids before cataract surgery. Our previous analyses have demonstrated how intravitreal steroids in the management of RVO are associated with more severe disease, more frequent macular changes affecting vision (pigmentary changes, epiretinal membrane or macular hole) and cataract.[6] It follows that a study on cataract in RVO has similar associations. We accounted for this when matching so that similar rates of steroid use were present in the operated and matched cohorts.

Cataract extraction is a well standardised, safe surgical procedure that delivers very good visual outcomes in

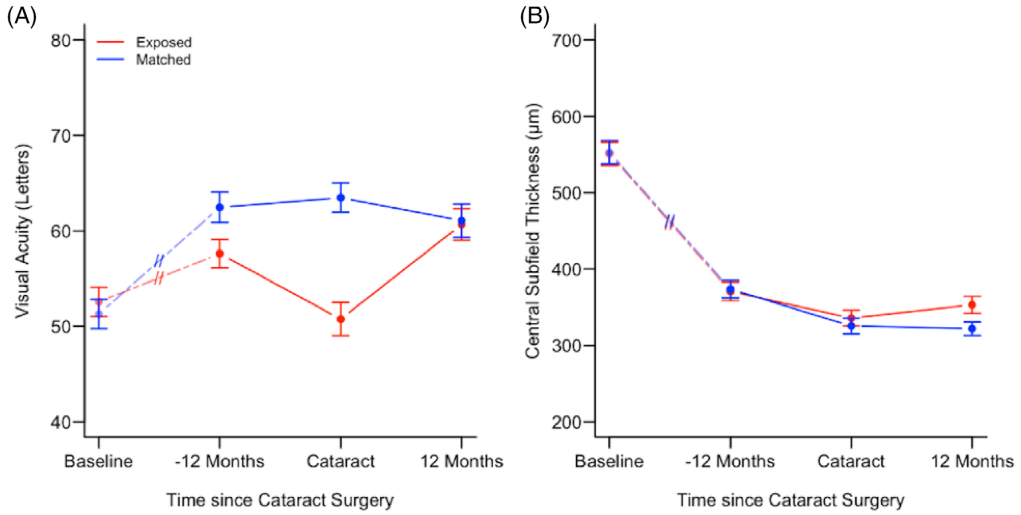

FIGURE 1 Mean (A) visual acuity and (B) central subfield thickness for eyes exposed to cataract surgery (red) and matched eyes (blue) at baseline (first intravitreal injection visit), 12 months before surgery, at cataract surgery, and 12 months after surgery.

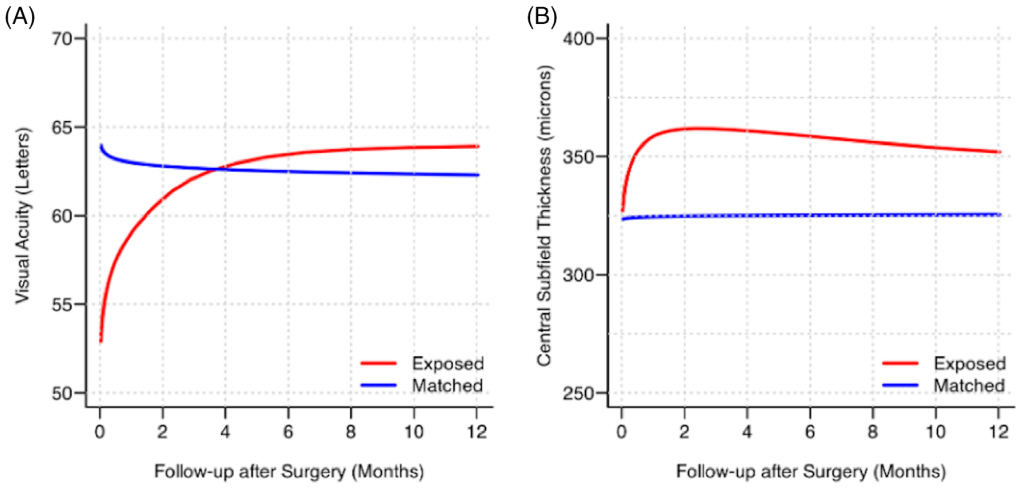

FIGURE 2 LOESS (locally weighted scatterplot smoothing) of mean (A) Visual acuity and (B) Central subfield thickness during the 12 months following cataract surgery in eyes exposed to cataract surgery (red) and matched eyes (blue). This non-parametric statistical approach allows graphical representation of the relationship between two variables where observation intervals are variable in number and frequency over time. It is especially useful for large datasets, where non-linear trends can be hard to visualise. The smoothed line is fit using local regression.

otherwise healthy eyes.[9] In a recent large study Ponder et al. reported visual improvement in RVO eyes undergoing cataract surgery, but they did not focus on those undergoing treatment for macular edema.[13] These subset is at higher risk of surgical complications.[10] Their vitreous composition is altered by the multiple intravitreal injections received,[17] their blood-retinal barrier is already compromised[18] and thus more vulnerable to the inflammation associated with surgery.[10]

While complicated surgeries are not tracked in the FRB! registry, we found that eyes undergoing surgery had very good visual outcomes and their VA equalised that of matched unoperated eyes 12 months after surgery. The final VA in our population was slightly lower than that reported by Ponder et al.[13] (0.5 vs. 0.4 LogMAR), but this gap is likely explained by the fact that all our patients were under treatment for CMO at the time of surgery while in the abovementioned study CMO developed only

TABLE 3 Predictive factors for visual acuity change 12 months after cataract surgery.

	Gained ≥15 letters	Gained 1–14 letters	No gain or lost >1 letter	*p* Value
Eyes	65	84	44	
Age at cataract, mean (SD)	74.2 (8.9)	73.1 (9.6)	71.8 (10.8)	0.45
Hypertension				
Present	40 (62%)	57 (68%)	30 (68%)	0.72
Absent	17 (26%)	21 (25%)	11 (25%)	
Unknown	8 (12%)	6 (7%)	3 (7%)	
RVO type				
BRVO	42 (65%)	43 (51%)	24 (55%)	**0.01**
CRVO	23 (35%)	41 (49%)	20 (45%)	
VA at cataract, mean (SD)	35.6 (22.4)	56.7 (22.4)	61.8 (18.7)	**<0.01**
CST at cataract, mean μm (SD)	328 (127)	336 (148)	348 (162)	0.25
Details of prior RVO treatment at time of surgery				
Duration of treatment, days, median (Q1, Q3)	974 (555, 1254)	874 (510, 1378)	820 (560, 1022)	0.82
Total injections, median (Q1, Q3)[a]	13 (9, 22)	11 (7, 18)	9 (7, 17)	0.32
Intravitreal steroid used, *n* (%)	26 (40%)	21 (25%)	15 (34%)	0.91
Last treatment interval, median (Q1, Q3)	56 (31, 93)	70 (30, 174)	110 (38, 212)	0.19
Last treatment active CME, *n* (%)	33 (51%)	39 (46%)	26 (59%)	0.14
New macular changes, *n* (%)	16 (25%)	11 (13%)	9 (20%)	0.89
Neovascular complications, *n* (%)	3 (5%)	9 (11%)	5 (11%)	0.08
PRP/sectoral laser, *n* (%)	19 (29%)	23 (27%)	12 (27%)	0.47
Focal laser, *n* (%)	8 (12%)	11 (13%)	3 (7%)	0.85

Note: Bold indicate statistically significant values.

Abbreviations: BRVO, branch retinal vein occlusion; CME, central macular edema; CRVO, central retinal vein occlusion; CST, central subfield thickness; neovascular complications, any posterior or anterior segment neovascularisation during the study; new macular changes, pigmentary changes, epiretinal membrane or macular hole noted during the relevant time period of the study; PRP, panretinal photocoagulation; Q1, first quartile; Q3, third quartile; SD, standard deviation; VA, visual acuity.

[a]Total injections include VEGF inhibitors and steroids.

in about 3% of the RVO population after cataract extraction.[13]

Like any other intraocular surgery, phacoemulsification induces a degree of intraocular inflammation that causes clinically significant macular oedema after 0%–6% of procedure.[19] While this alteration is transient and usually resolves completely in otherwise healthy eyes, there is concern that it could exacerbate macular oedema secondary to other clinical conditions like RVO or diabetes.[10,19]

Cho et al, reported postsurgical CMO to occur in about 27.4% of RVO eyes that had a dry macula for at least 6 months prior to cataract extraction.[11] Similarly Starr et al. reported a transient increase in the CST of eyes treated for CMO secondary to RVO following cataract surgery. These data highlight the fragility of these population.[12] In the current study, we found that RVO eyes exposed to cataract surgery had a significantly higher CST compared with unexposed matched eyes 12 months after surgery, despite receiving more injections than the unoperated matches. We plotted the postoperative VA and CST using Loess regression and found an elevation in CST almost immediately following surgery only partially resolving through 12 months. This suggests that surgically induced inflammation[20] may modestly increase macular oedema in RVO eyes without significantly affecting long term VA outcomes.

The increase of macular oedema following cataract extraction also likely explains the significantly higher injection frequency observed in operated eyes in the 12 months following the procedure compared with controls. The higher number of injections could also depend on a tendency to overtreat to prevent anticipated exacerbation of the underlying CMO following surgery, although this seems less than adequate because the eyes that underwent surgery still had more swelling than those that did not. Starr et al. reported no impact on the number of injections in their eyes that experienced

increase in CST following cataract extraction.[12] This seems in contrast with our observations, but the very small number of eyes included in their study and the monocentric nature of their study makes their results hardly comparable to ours.

Matching ensured groups had similar utilisation of VEGF inhibitors and steroid implants prior to surgery but we observed a small but significant shift towards steroids after cataract surgery. Clinicians may have been more inclined to use steroids after surgery suspecting an inflammatory component contributing to increased macular oedema.[21] In addition, the eyes that were now pseudo-phakic may have been considered better candidates for steroid treatment.[22] Steroid implants may last longer than VEGF inhibitors. This may have further augmented the intensity of treatment in operated eyes that already received numerically more frequent injections than unoperated eyes after 'surgery'.

We found that lower VA and having BRVO (rather than CRVO) predicted significantly greater change in VA after cataract surgery (Table S1). In some eyes, VA may have been reduced more by the lens opacity than the underlying retinal disease. Cataract surgery was performed in BRVO and CRVO when VA was reasonably similar (BRVO 55.2, CRVO 51.4 letters). The mean VA equalised after surgery with their respective matched cohorts. The larger gain in VA in BRVO is consistent with realising a greater visual potential compared with CRVO once the cataract is removed.[6,23]

Surgery was performed well after the induction phase of therapy at a median of 2.6 years with reasonably low mean CST of 336 microns compared with baseline CST of 551 microns. It is reassuring that even if CST fluctuated after cataract extraction just a few extra injections in the 12 months after surgery allowed for good visual outcomes in most eyes. Interestingly age, history of hypertension, prior neovascular complications, macular changes affecting vision or treatment with laser appeared to have no effect on final VA.[8]

Our study has some limitations. Like all FRB! studies, treatment criteria are not standardised and remain completely up to the treating physician. For this reason, while we matched our two groups by first injection agent, by number of VEGF injections and separately by number of steroids, we could not control for treatment regimen, comparisons between different drugs or treatment strategies could not be performed. Cataract can affect refraction and consequently VA. FRB! users are asked to fill the register with the best among corrected, uncorrected or pinhole. While we cannot assure this was done in all cases, the method of measurement was likely consistent along with any effect on change in VA. Complicated cataract surgery and cataract grading are not specifically tracked in the RVO module of the FRB! registry thus we could not investigate neither the impact of cataract severity on clinical outcome nor if eyes with RVOs undergoing cataract extraction had a higher incidence of surgical complications. Surgical technique is not recorded in the module either, but we can assume that the majority of eyes received phacoemulsification and if other techniques were used their impact on the analysis would be minimal given the very limited percentage of cases. Finally, the FRB! registry does not include images, only the CST is recorded, thus our analysis could not assess the impact of qualitative imaging features on functional outcomes in this setting.

To conclude, in this large real-world observational study we found that cataract extraction compared with a matched cohort that did not have cataract delivered good visual outcomes in patients being treated for macular oedema secondary to RVO. Pre-operative injection frequency, CST and duration of therapy since first injection had no significant impact on VA at 12 months after surgery, while lower VA at the time of surgery and BRVO were associated with better VA gains. More injections on average seem to be required in the 12 months after surgery for eyes to reach VA values comparable to those of unoperated matched eyes.

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CONFLICT OF INTEREST STATEMENT

Disclosure statements can be found in the supplementary material.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE-CLINICAL SCIENCE OPEN ACCESS

Outliers of Treatment Frequency in Retinal Vein Occlusion: 24-Month Comparative Analysis of Fight Retinal Blindness! Practitioners

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Keywords: BRVO | CRVO | macula | occlusion | oedema | retinal | treatment frequency | vein

ABSTRACT

Background: We aimed to describe a 2-year outcome of eyes managed by practitioners benchmarked using a funnel plot by their frequency of treatment using vascular endothelial growth factor (VEGF) inhibitors for naive retinal vein occlusion (RVO).

Methods: A multicentre, international, observational study of 29 doctors in 12 countries managing 1110 eyes with RVO commencing VEGF inhibitors between 1 January 2012–2022 tracked in the Fight Retinal Blindness! registry.

Results: We identified 3 outlying 'intensive' practitioners (managing 350/1110 eyes [32%]), 22 'typical' practitioners (604/1110, [54%]) and 4 outlying 'relaxed' practitioners (156/1110, [14%]) with respective 24-month outcomes in Branch and Central RVO including the primary outcome, mean adjusted change in visual acuity (VA) in BRVO: +16.2, +13.6, +9.3 letters ($p < 0.01$) and CRVO: +14.2, +12.7, +4.8 letters ($p < 0.01$); adjusted change in macular thickness in BRVO −179, −150, −159 μm ($p < 0.01$) and CRVO −324, −283, −232 μm ($p < 0.01$); time-in-range with VA > 68 letters in BRVO 90, 78, 68 weeks ($p < 0.01$) and CRVO 69, 60, 54 weeks ($p = 0.04$); median injections 18, 13 and 10; median final injection intervals, BRVO 6, 9, 10 weeks and CRVO 6, 9 and 12 weeks; with no significant difference in adverse outcomes.

Conclusions: At 24 months, the intensive practitioners were treating RVO using VEGF inhibitors with twice the frequency of the relaxed practitioners; however, their patients had gained twice (BRVO) to three times (CRVO) more letters of VA.

Abbreviations: BRVO, branch retinal vein occlusion; CI, confidence interval; CRVO, central retinal vein occlusion; CST, central subfield thickness; FRB!, Fight Retinal Blindness!; GAMMs, generalised additive mixed effects models; IRB, Institutional Review Board; LogMAR, logarithm of the minimum angle of resolution; MO, macular oedema; OCT, optical coherence tomography; RCT, randomised controlled trial; RWE, real-world evidence; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.

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[Correction added on 09 January 2025, after first online publication: The copyright line was changed.]

1 | Introduction

There is likely a range of treatment intensities amongst practitioners using vascular endothelial growth factor (VEGF) inhibitors to treat retinal vein occlusion (RVO) based on their interpretation of the evidence, regional differences in access and their individual patient's tolerance of the treatment burden.

Existing real-world evidence has suggested a strong relationship between treatment frequency and visual acuity (VA) outcomes in RVO; however, disease severity likely contributed to that association [1]. Grouping in that evidence was by the number of injections that eyes received. The top end of injection frequency was overpopulated by eyes with lower vision and the lower end by eyes with less severe disease. This approach may have exaggerated the benefits of frequent VEGF inhibitor injections for RVO because eyes with severe disease can have very large gains in VA, whereas eyes with mild disease are limited by a 'ceiling' effect [2]. Quantifying the effect of treatment frequency in isolation would be better achieved if the groups were otherwise similar at baseline, each with a representative mix of patients typically encountered in routine practice.

This study used data from the Fight Retinal Blindness! (FRB!) registry to compare outcomes in patients 24 months after commencing VEGF inhibitors for treatment-naïve RVO based on the benchmarked mean treatment frequency of their treating physician. Grouping by the treatment frequency of practitioners rather of individual eyes, along with adjustment for VEGF inhibitor utilisation and baseline difference in cohorts, aimed to minimise the confounding effect of disease severity seen in previous reports.

2 | Methods

2.1 | Design and Setting

This was a multicentre international observational study analysing the effect of the mean practitioner treatment frequency on 24-month outcomes in treatment-naïve eyes with RVO commencing VEGF inhibitors tracked in the FRB! registry. The registry is accessed free of charge via a web-based interface or, in some centres, through automatic electronic medical record (EMR) integration [3]. The data in FRB! are of high quality, consisting of a pre-specified minimum dataset from each visit that is only accepted when it is 100% complete and within pre-specified ranges. There is no option for free text; all inputs are mutually exclusive, numeric or from drop-down menus. FRB! users agree to track at least 85% of the patients they managed with the relevant condition. As the caseload of individual physicians increases, they are more likely to be managing a representative sample of the diversity of patients encountered in real-world practice.

The FRB! registry is observational, in no way modifying the treatment decisions made by participating clinicians in consultation with their patients. Data pertaining to each visit are entered very quickly or automatically if integrated with the EMR. The baseline FRB! visit records demographic details, ocular conditions, details of pretreatment, ischaemic angiography findings and presence of glaucoma. Subsequent FRB! visits record VA in the most letters read on a logarithm of minimum angle of resolution (LogMAR) acuity chart (best of unaided, aided or pinhole), intraocular pressure, central subfield thickness (CST, in microns), the presence or absence of macular oedema (MO) judged by the treating physician, treatment given at that visit, RVO complications, procedures that day or since the last visit, adverse events and discontinuation of treatment reasons recorded when necessary with additional drop-down menus.

Ethics and data protection were granted by the Royal Australian and New Zealand College of Ophthalmologists (HREC#16.09); Société Française d'Ophtalmologie, France (2017_CLER-IRB_ll-05); Mater Private Network Dublin IRB, Ireland (1/3788/2130); The Area 1 Milan Ethical Committee; Academic Medical University Centre (non-interventional approval), Netherlands; Comissão de Ética para a Saude. Centro Hospitalar e Universitário de Coimbra, Portugal; Etická komisia UN-Nemocnica svätého Michala, Slovakia; The Spanish IRB (Comité Etico de Investigación Medica, Hospital Clínic de Barcelona), Spain; The Cantonal Ethics Committee Zurich; and the Caldicott Guardian at the Royal Free London NHS Foundation Trust, UK. This observational study adhered to the STROBE checklists [4], the Declaration of Helsinki tenets, and 'opt-in' written consent was provided in European centres and 'opt-out' in Australia and New Zealand.

2.2 | Patient Selection and Definitions

Eligible eyes were treatment-naïve with MO due to RVO commencing treatment between 1 January 2012 and 1 January 2022 with either bevacizumab (1.25 mg Avastin; Genentech Inc., CA, USA/Roche, Basel, Switzerland), aflibercept (2 mg Eylea, Bayer) or ranibizumab (0.5 mg Lucentis, Genentech Inc/Novartis); they must have received at least three injections of 'VEGF monotherapy' and had at least 1 year of follow-up (365 days) to establish treatment frequency. Eyes were excluded if they received steroids in the first year; otherwise, observations were censored after switching to steroids if it occurred in the second year. The study period was from the first treatment to the 2-year visit closest to 730 days (2 years ± 90 days). 24-month 'completers' were defined by having a 2-year visit. The study focused on eligible practitioners (> 5 eligible eyes), meaning that some otherwise eligible eyes were excluded.

2.3 | Outcomes

We isolated treatment frequency as the main uncontrolled variable by grouping practitioners rather than eyes, since an individual practitioner's general treatment aggression presumably remains reasonably constant irrespective of disease severity. Nevertheless, we adjusted outcomes to account for any baseline demographic differences between practitioner cohorts and for

their individual practitioners' preference or limited availability to use certain VEGF inhibitors in patients that they managed.

The primary outcome was the mean adjusted change in VA from baseline to 24 months. Secondary outcomes included the mean adjusted change in CST; percentages with final VA ≥ 70 or ≤ 35 letters, and VA gain or loss ≥ 15 letters; time-in-range with VA > 68 letters (weeks), final interval between injections, visits and injections, 24-month completion, laser treatments and adverse events.

2.4 | Statistical Analysis

Clinical registries typically use funnel plots to detect poor outcomes due to atypical practice patterns of individuals that then trigger quality improvement in a learning health system through feedback [5]. Here, we used funnel plots to benchmark the average treatment frequency of individual FRB! practitioners [6]. We wanted to identify outliers with great confidence by using a 99.7% confidence interval (CI). The benefit of using a funnel plot to identify outliers, rather than standard deviation (SD) or quartiles, comes from the incorporation of statistical power through caseload; i.e., practitioners managing a large caseload would be less vulnerable to runs of severe or mild disease affecting their mean treatment frequency compared with practitioners managing only a few cases. The higher the caseload, the less likely that practitioners' treatment frequency is confounded by such bias.

Generating the funnel plot involved first plotting the mean treatment interval of eyes managed by each practitioner on the *y*-axis against caseload on the *x*-axis. Then, a 99.7% confidence limit (CI) at 3.0 standard errors above and below the overall mean was applied, forming the funnel that narrows with increasing caseload. This is because the standard error is the SD divided by the square root of caseload. Practitioners outside the predicted confidence limit were identified as 'intensive' or 'relaxed' outliers of treatment frequency. The mean interval between injections through 24 months for each eye was calculated after loading—either after 6 months of treatment or earlier if graded as having a resolution of MO within 6 months by the treating physician.

The adjusted VA (or CST) for BRVO and CRVO was analysed separately for each treatment frequency group from baseline to 24 months using generalised additive mixed effects models (GAMMs). The models were adjusted for which the VEGF inhibitor was initiated, baseline VA (or CST), age and nesting in bilateral cases. The outputs from these models were plotted over 24 months and provided the 24-month adjusted outcomes including the mean adjusted change in VA (the primary outcome) and the mean adjusted change in CST. Time-in-range was the mean number of weeks that eyes in each group spent with VA > 68 letters, as previously described by Kozak et al. in eyes treated with VEGF therapy for diabetic macular edema [7].

Crude demographic and outcome data were summarised with counts, percentages, means, SDs or CIs, and where appropriate, medians with first and third quartiles (Q1, Q3). Statistical analysis was performed using R version 4.2.2 (http://www.R-project.org/), utilising the *mgcv* (V1.9-1) for GAMMs [8].

3 | Results

3.1 | Patient Characteristics and Disposition

We identified 1110 eyes (587 BRVO [53%], 523 CRVO [47%]) managed by 29 practitioners eligible for this analysis in 12 countries (Australia, France, Ireland, Italy, Netherlands, New Zealand, Portugal, Slovakia, South Africa, Spain, Switzerland and United Kingdom). Five hundred and seventy-six otherwise eligible eyes were excluded from the analysis because they received ≤ 2 injections, received steroids in the first year, follow-up was ≤ 12 months or their physician had tracked fewer than five eyes with RVO in the registry.

A funnel plot identified the eligible practitioners outside the 99.7 CI as outliers of treatment frequency, including three 'intensive' and four 'relaxed' practitioners with the mean interval between injections more than 3 standard errors (99.7% CI) above or below the overall mean (Figure 1).

The 'intensive' outliers managed 350/1110 eyes (31%), the 'relaxed' outliers managed 156/1110 eyes (14%), while the remaining 22 practitioners labelled 'typical' managed 604/1110 eyes (54%). One practitioner was only eligible for BRVO. Table 1 describes the baseline characteristics of the eyes grouped by the treatment frequency of their practitioner. The BRVO 'intensive' group had higher baseline VA ($p < 0.01$) and lower baseline CST ($p = 0.03$) compared with the BRVO 'typical' and 'relaxed' groups. The characteristics of the CRVO groups were broadly similar. Bevacizumab was the commonest choice of the initial VEGF inhibitor for eyes in the 'intensive' group and ranibizumab for those in the 'typical' or 'relaxed' groups ($p < 0.01$, Table 1). In keeping with the routine practice, this cohort included 293/1110 eyes (26%) with baseline VA below or above the typical inclusion criteria of major trials (19–73 letters) [2, 9–14].

3.2 | Visual and Anatomical Outcomes

The primary outcome of the adjusted mean change in VA for 'intensive', 'typical' and 'relaxed' groups with BRVO was +16.2, +13.6, and +9.3 letters ($p < 0.01$) and with CRVO, it was +14.2, +12.7, and +4.8 ($p < 0.01$), respectively (Table 2, Figure 2). The adjusted mean change in CST for 'intensive', 'typical' and 'relaxed' groups with BRVO was −179, −150, and −159 μm ($p < 0.01$), respectively; with CRVO, it was −324, −283, and −232 μm ($p < 0.01$), respectively. Adjustment of outcomes was applied to address the significant heterogeneity of utilisation of different VEGF inhibitors and for significant difference in baseline characteristics, particularly in the BRVO groups. Adjusted VA and adjusted CST are plotted in Figure 2. The unadjusted outcomes are also described in Table 2. In the subset of eyes in our cohort with baseline VA within the inclusion criteria of major RVO trials (19–73 letters), the adjusted mean change in VA for 'intensive', 'typical' and 'relaxed' groups with CRVO was +12.0, +9.1, and +0.6 letters ($p < 0.01$), and for BRVO, it was +17.7, +13.9, and +10.3 letters ($p < 0.01$), respectively.

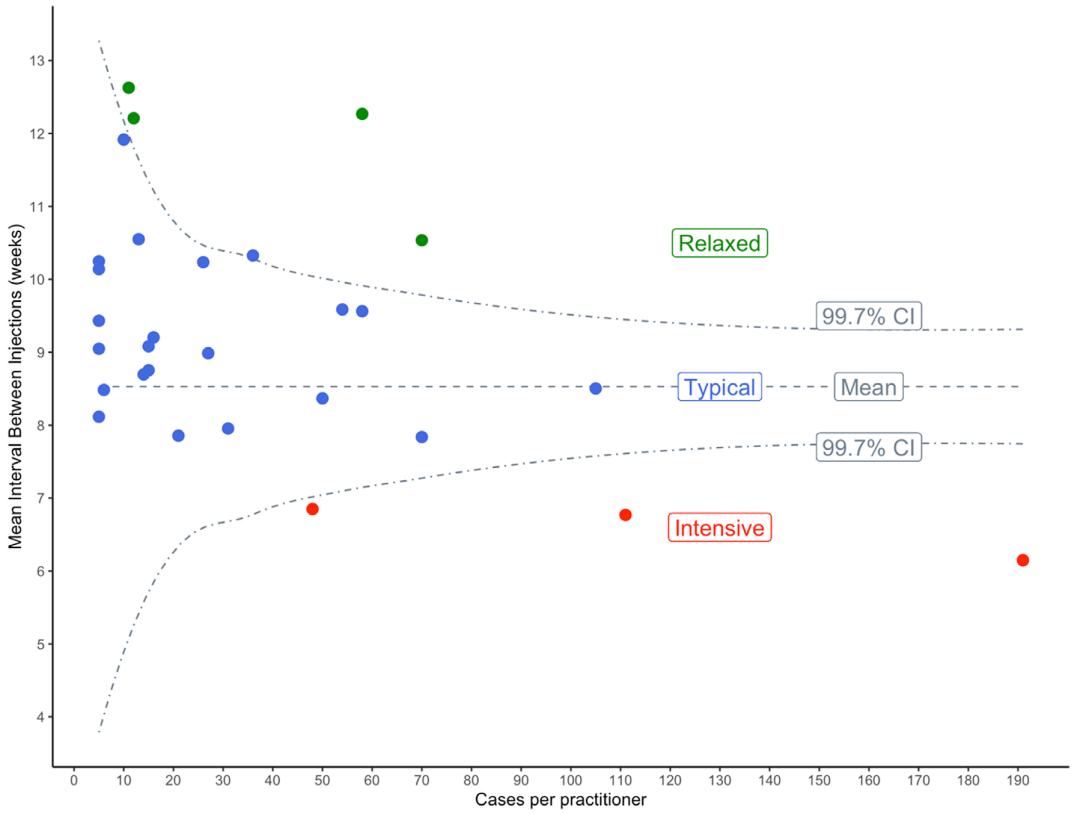

FIGURE 1 | Funnel plot identifying outliers of treatment frequency in RVO based on the mean treatment interval between injections in the patients that they managed. The central dashed line is the mean treatment interval of the entire cohort. The dot-dashed lines (the funnel) represent 3 standard errors (i.e., the 99.7% confidence interval) of deviation from the overall mean. The 'typical' (blue) practitioners fall within the funnel. Outlying practitioners including the 'intensive' (red) and 'relaxed' (green) practitioners fall outside the funnel.

3.3 | Time-in-Range Analysis

The proportion of eyes achieving VA > 68 letters at any point during the study was 89% in BRVO and 71% in CRVO, which was independent of treatment frequency ($p = 0.96$, $p = 0.16$, Table 2). In the subset of eyes that did achieve VA > 68 letters, it was the mean time-in-range that differed significantly between 'intensive', 'typical' or 'relaxed' groups for both BRVO (90, 78, 68 weeks [$p < 0.01$]) and CRVO (69, 60, 54 weeks [$p = 0.04$]).

3.4 | Injections, Visits and Treatments

In keeping with the study design, more frequent treatment groups had more injections, along with more visits and shorter final intervals between injections at 24 months (Table 2). This equated to around 80% more injections by 'intensive' practitioners compared with that of 'relaxed' practitioners. The completers in the 'intensive', 'typical' and 'relaxed' groups with BRVO received a median of 18, 12 and 10 injections, at 22, 16 and 18 visits and a median final treatment interval of 6, 9 and 10 weeks, respectively; the eyes with CRVO received a median of 18, 14 and 10 injections, at 22, 19 and 18 visits and a median final treatment interval of 6, 9 and 12 weeks at 24 months, respectively. In the second year of treatment, the median injections delivered in the 'intensive', 'typical' and 'relaxed' groups were in BRVO 7, 4 and 4 and in CRVO 8, 6 and 4, respectively.

Switching between VEGF inhibitors occurred in 214/1110 eyes (19%) at a median (Q1, Q3) of 276 days (169, 445). Switching occurred least in the relaxed groups ($p < 0.01$, Table 2). Laser treatment was delivered more frequently by the 'intensive' practitioners compared with that of the 'typical' or 'relaxed' practitioners including focal laser in BRVO (27%, 5%, 1% [$p < 0.01$]), sectoral laser in BRVO (20%, 16%, 12% [$p = 0.30$]) and PRP laser in CRVO (41%, 21%, 24% [$p < 0.01$]). Cataract surgery was performed more often in the BRVO 'relaxed' group compared with the 'typical' or 'intensive' BRVO groups (24%, 7%, 5% [$p < 0.01$]) but it was not significantly different in CRVO (17%, 8%, 10% [$p = 0.13$]).

3.5 | Non-Completion

The 24-month completion rate was 79% overall (877/1110), similar amongst the groups, but non-completers had less impressive outcomes. The outcomes were imputed in eyes that did not complete the study within the models. Nevertheless, at the final review, the 118/587 (20%) BRVO non-completers had gained a mean of +9 letters compared with +14 letters in BRVO completers ($p < 0.01$). The 115/523 (22%) CRVO non-completers gained +8 letters compared with +14 letters in CRVO completers (408/523 [78%]; $p = 0.05$). Reasons for non-completion were documented in 152/233 (65%) of non-completers: most were likely unrelated to poor outcomes, including (part of the 65%), 'going

TABLE 1 | Baseline demographics: BRVO and CRVO eyes grouped by the treatment frequency of the practitioner managing their care.

	BRVO (587 eyes)				CRVO (523 eyes)			
	Intensive	**Typical**	**Relaxed**	***p*[a]**	**Intensive**	**Typical**	**Relaxed**	***p*[a]**
Practitioners, *n*	3	22	4		3	21	4	
Eyes, *n*	161	337	89		189	267	67	
Patients, *n*	159	332	87		187	261	66	
Mean interval, weeks (SD)	6.3 (2)	9.1 (3.3)	11.5 (4)	**< 0.01**	6.6 (2.7)	8.7 (3.3)	11.5 (4.6)	**< 0.01**
VA, letters (SD)	62.2 (17)	57.2 (17.3)	57.8 (17.7)	**< 0.01**	41.7 (26.5)	44.4 (25.4)	47.1 (21.4)	0.27
≤ 35 letters, %	7%	13%	16%	0.10	39%	36%	30%	0.44
≥ 70 letters, %	42%	28%	37%	**< 0.01**	16%	16%	16%	0.99
CST, μm (SD)	446 (134)	485 (171)	453 (161)	**0.03**	610 (246)	614 (237)	610 (220)	0.91
Age, years (SD)	70 (12)	71 (11)	72 (10)	0.12	71 (12)	72 (12)	70 (11)	0.65
Gender, % female	55%	56%	55%	0.98	43%	42%	45%	0.92
Initial injection				**< 0.01**[b]				**< 0.01**[b]
Bevacizumab, %	116 (72%)	90 (27%)	6 (7%)		93 (49%)	43 (16%)	7 (10%)	
Ranibizumab, %	23 (14%)	128 (38%)	49 (55%)		52 (28%)	111 (42%)	33 (49%)	
Aflibercept, %	22 (14%)	119 (35%)	34 (38%)		44 (23%)	113 (42%)	27 (40%)	

Note: P values < 0.05 (bold) were considered significant.

Abbreviations: BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, CST = central subfield thickness, *n* = number, SD = standard deviation, VA = visual acuity.

[a]*p*-values were otherwise derived using analysis of variance (ANOVA).

[b]Chi-square test on 3 × 3 contingency tables.

to another doctor' (16%), 'treatment success' (13%) and 'deceased' (24%), while some were likely related to a poor outcome including 'futility of treatment' (5%), 'medical contraindication' (1%) and 'patient declined treatment' (5%).

3.6 | Maximum and Minimum Treatment Frequencies

The single most intensive practitioner in our study achieved better visual outcomes than other intensive practitioners. This prompted a post hoc analysis, of the 350/1110 eyes (32%) in the intensive group, that compared the single most intensive practitioner with the two other intensive practitioners (Tables 3 and 4). The most treatment-intensive practitioner commenced treatment with bevacizumab exclusively, in 191 eyes with significantly higher baseline VA (BRVO; $p = 0.03$, CRVO; $p = 0.03$) than other intensive practitioners treating 159 eyes. The most treatment-intensive practitioner delivered higher median injections compared with other intensive practitioners in both BRVO and CRVO over the 2-year study (20 vs. 16; $p < 0.01$, 21 vs. 15; $p < 0.01$). In the second year, the most treatment-intensive practitioner delivered a median of eight injections in BRVO and nine in CRVO. The single most intensive practitioner treated 39% of BRVO eyes under their care with focal laser, whereas other intensive practitioners treated only 5% of BRVO eyes. The mean final VA in eyes treated by the most treatment-intensive practitioner was higher in BRVO (79 vs. 72 letters; $p < 0.01$) and CRVO (66 vs. 51 letters; $p < 0.01$), including significantly fewer eyes with final VA ≤ 35 letters (BRVO $p = 0.05$, CRVO $p = 0.01$) compared with other intensively treated eyes. The time-in-range (weeks, VA > 68 letters) was higher in CRVO eyes treated by the most intensive practitioner than that in other intensive CRVO eyes (74% vs. 63%; $p = 0.04$). The 24-month anatomic outcomes were similar between members of the intensive group with CRVO or BRVO. We analysed the outcomes of relaxed practitioners in a similar way but found outcomes similar amongst the relaxed practitioners.

3.7 | Adverse Events

Neovascular complications in either the anterior or posterior segment occurred in 58/1110 eyes (5%). The neovascular complications occurred at similar rates in the 'intensive', 'typical' and 'relaxed' groups with BRVO (1%, 3%, 2% [$p = 0.55$]) and CRVO (6%, 10%, 9% [$p = 0.27$]), though eyes managed by the most treatment-intensive practitioner had very low rates (BRVO 0%, CRVO 2%). There were 11 eyes with CRVO that developed rubeosis unrelated to treatment frequency ($p = 0.77$), and the mean final VA was seven letters; all were treated with PRP laser. New macular changes including epiretinal membrane, macular hole, pigment change or atrophy occurred during the study at similar or sporadic rates in the 'intensive', 'typical' and 'relaxed' groups with BRVO (10%, 10%, 8%; $p = 0.84$) and CRVO (19%, 11%, 20%; $p = 0.02$). The mean final VA in eyes with new macular changes was 60 letters in BRVO and 40 letters in CRVO. Of 14 518 injections delivered in the study, there were four cases

TABLE 2 | 24-month outcomes: BRVO and CRVO eyes grouped by the treatment frequency of the practitioner managing their care.

	BRVO (587 eyes)				CRVO (523 eyes)			
	Intensive	**Typical**	**Relaxed**	***p***	**Intensive**	**Typical**	**Relaxed**	***p***
Eyes, *n*	161	337	89		189	267	67	
Completers, *n* (%)	133 (83%)	271 (80%)	65 (73%)	0.18	154 (81%)	202 (76%)	52 (78%)	0.34
Initial VA, mean (SD), letters	62.2 (17)	57.2 (17.3)	57.8 (17.7)	**<0.01**	41.7 (26.5)	44.4 (25.4)	47.1 (21.4)	0.27
Final VA, mean (SD), letters	76.6 (14.5)	70.2 (16.1)	66.9 (17.4)	**<0.01**	57.6 (27.4)	56.8 (25.3)	50.3 (24)	0.13
≤35 letters, %	3%	4%	10%	0.05	22%	19%	22%	0.78
≥70 letters, %	80%	68%	62%	**<0.01**	46%	38%	27%	**0.02**
Gain ≥15 letters, %	48%	40%	35%	0.10	51%	45%	36%	0.10
Loss ≥15 letters, %	1%	4%	9%	**0.01**	8%	12%	22%	**0.01**
ΔVA, mean (95% CI), letters	+14 (12, 17)	+13 (11, 15)	+9 (5, 13)	0.06	16 (12, 19)	12 (9, 16)	3 (−3, 9)	**<0.01**
Adjusted Δ VA mean (95% CI), letters[a]	+16.2 (14.3, 18.2)	+13.6 (12.0, 15.2)	+9.3 (6.6, 12.0)	**<0.01**	+14.2 (10.4, 18.0)	12.7 (9.4, 16.0)	4.8 (−0.6, 10.3)	**<0.01**
Final CST, mean (SD), μm	278 (56)	307 (96)	300 (142)	**<0.01**	292 (123)	335 (171)	361 (188)	**<0.01**
Δ CST, mean (95% CI), μm	−168 (−191, −145)	−177 (−197, −157)	−154 (−196, −111)	0.54	−319 (−357, −281)	−280 (−312, −247)	−248 (−314, −183)	0.15
Adjusted Δ CST, mean (95% CI), μm[a]	−179 (−166, −193)	−150 (−138, −163)	−159 (−142, −176)	**<0.01**	−324 (−299, −349)	−283 (−263, −302)	−232 (−199, −265)	**<0.01**
Injections, median (Q1, Q3)[b]	18 (14, 23)	12 (9, 16)	10 (7, 12)	—	18 (12, 23)	14 (11, 17)	10 (7, 12)	—
Last interval, median (Q1, Q3) weeks[b]	6 (4, 10)	9 (6, 13)	10 (7, 17)	—	6 (4, 10)	9 (7, 12)	12 (9, 17)	—
Visits, median (Q1, Q3)[b]	22 (17, 26)	16 (13, 20)	18 (15, 21)	—	22 (18, 26)	19 (16, 23)	18 (16, 22)	—
Visits with injections, %	82%	72%	57%	**<0.01**	75%	70%	57%	**<0.01**

(Continues)

TABLE 2 | (Continued)

	BRVO (587 eyes)				CRVO (523 eyes)			
	Intensive	Typical	Relaxed	*p*	Intensive	Typical	Relaxed	*p*
Time-in-range (TIR)[c]								
Achieved VA > 68 letters, %	88%	89%	89%	0.96	68%	74%	63%	0.16
TIR, weeks, mean (% weeks)	90 (87%)	78 (76%)	68 (67%)	**< 0.01**	69 (67%)	60 (58%)	54 (51%)	**0.04**
Switched VEGF inhibitor, *n* (%)	34 (21%)	77 (23%)	11 (12%)	**< 0.01**	41 (22%)	44 (16%)	7 (10%)	**< 0.01**

Note: *P* values < 0.05 (bold) were considered significant.

Abbreviations: BRVO = branch retinal vein occlusion, CI = confidence interval, CRVO = central retinal vein occlusion, CST = central subfield thickness, *n* = number, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, TIR = time-in-range (VA > 68 letters), VA = visual acuity, VEGF = vascular endothelial growth factor.

[a]Adjusted for baseline VA, CST, age, initial VEGF inhibitor and nesting in bilateral cases using generalised additive mixed effects models.

[b]Calculated in 24-month completers, but *p*-values were not calculated as the groups were formed based on the difference in these parameters.

[c]Includes completers that achieved > 68 letters within the study duration, mean time expressed in weeks and as a mean percentage of the 104-week study. The p-values were derived using the analysis of variance (ANOVA) for continuous variables.

of infectious endophthalmitis (rate: 0.03%, one 'intensive', three 'typical'), three cases of non-infectious endophthalmitis (rate: 0.02%, one 'intensive', one 'typical'), one retinal detachment (rate: 0.01%, 'typical'), but no recorded cases of intraocular inflammation or vasculitis.

4 | Discussion

We found the funnel plot helpful in categorising the relative treatment frequency of practitioners commencing VEGF inhibitors for treatment-naïve RVO in routine care over 24 months. Patients who saw practitioners who on average performed more injections gained more letters compared to those practitioners who treated less. One highly intensive practitioner clearly had superior results to any other. On the one hand, these findings suggest that the funnel plot can be used to identify and notify relaxed practitioners of their status benchmarked against their peers. On the other, the superior outcomes of the intensive practitioners indicate what is achievable with the more frequent VEGF inhibitor therapy for RVO routine care.

The primary outcome of the adjusted 24-month mean change in VA from baseline was significantly greater with more frequent treatment of both CRVO ('intensive': +14.2, 'typical': +12.7, 'relaxed': +4.8 letters; $p < 0.01$) and BRVO (+16.2, +13.6, +9.3 letters; $p < 0.01$). The mean adjusted 24-month change in CST was significantly greater with more frequent treatment of both CRVO (−324, −283, −232 μm; $p < 0.01$) and BRVO (−179, −150, −159 μm; $p < 0.01$).

As anticipated from the study design, the frequency of injections was higher in eyes treated by 'intensive' practitioners compared with that in 'relaxed' practitioners (median injections, 18 vs. 10). At 24 months, the 'intensive' groups were being treated with nearly twice the frequency of eyes in the 'relaxed' groups (final mean treatment interval, 6 weeks vs. 10–12 weeks). Visits were only modestly more frequent by group over the entire 24 months (median, 22 in 'intensive' vs. 18 in 'relaxed' groups). It was the higher proportion of visits at which treatment was given in the intensive group (75%–80% visits), compared with that in the relaxed group (57% visits), which really lifted the overall treatment frequency. One could argue that burden is not only measured by injection numbers but also by the number of times patients and their caregivers have to attend for review.

Eyes with very poor VA can often have very large improvements in VA [15]. Most RVO trials required baseline VA between 19 and 73 letters for inclusion [2, 9–14]. Considering only the subset of our cohort with 'trial-eligible' baseline VA, we found that this subset when treated with an 'intensive' regimen achieved gains (CRVO: +12.0 letters, BRVO: +17.7 letters) comparable to those of the RCTs (CRVO: +10 to +16 letters, BRVO: +15 to +18 letters) [13, 16–21], whereas 'typical' and 'relaxed' regimens were associated with less impressive outcomes more typical of evidence derived from routine care [14, 19, 22–25].

The trend for better outcomes with increasing treatment frequency extended up to the single most intensive practitioner. The most intensive practitioner managed 191 eyes with RVO, maintaining high rates of a 2-year completion (87%–93%). We

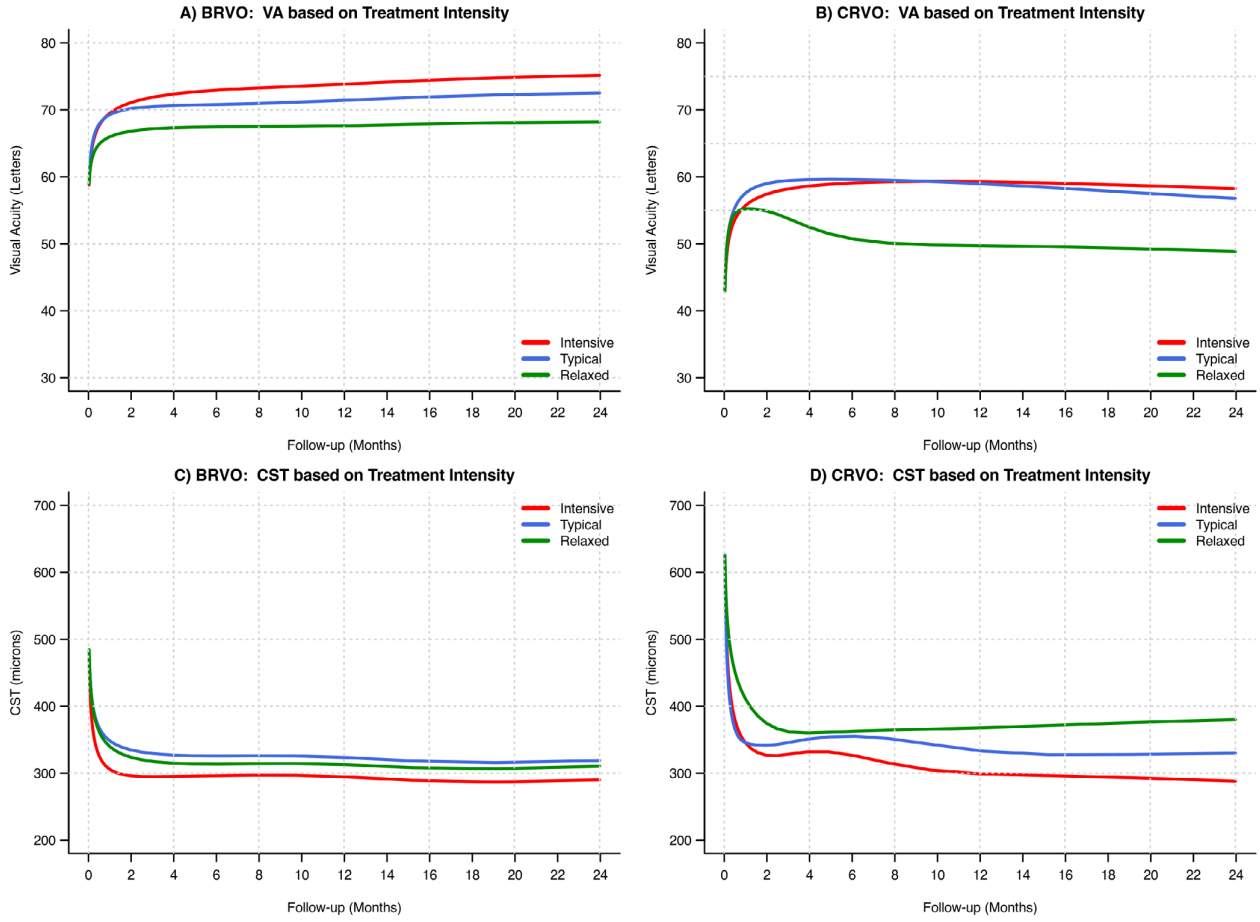

FIGURE 2 | Adjusted mean visual acuity (VA) and central subfield thickness (CST) through 24 months by the RVO type (branch: BRVO or central: CRVO) and grouped by treatment frequency of the practitioner managing their care. Adjustment was performed using generalised additive mixed effects models (GAMMs) accounting for difference in the initial VEGF inhibitor, baseline VA (or CST), age and nesting in bilateral cases.

were surprised by the exceptionally large gains in VA observed in these eyes, particularly as they had higher baseline VA, along with greater likelihood of a ceiling effect limiting outcomes, when compared with other intensively treated (CRVO: 46 vs. 38 letters, BRVO: 64 vs. 58 letters). Eyes treated by this most intensive practitioner achieved a mean change in VA of +20 letters from baseline in CRVO by treating at 88% of 22 visits, whereas the other intensive practitioners reviewed their patients as frequently but treated with more likely a pro-re-nata approach (70% of 21 visits involved treatment) to achieve the mean change in VA of +13 letters. The most intensive practitioner applied a similar frequency of treatment in eyes with BRVO, matching the mean change in VA (14–15 letters) of other intensive practitioners despite the higher baseline VA.

A trait of the 'intensive' outliers was the maintenance of frequent treatment through the second year of the 24-month study. Trial evidence has demonstrated how a more relaxed regimen in the second year can erode outcomes. The SCORE2 study reported mean changes in VA at 12 months in CRVO (including Hemi-RVO) with aflibercept or bevacizumab of +21.6 and +21.7 letters, but those early gains had eroded to +14.2 letters at 24 months, with reduced treatment frequency in the second year (3.6–4.6 injections, from 12 to 24 months)—a frequency of treatment that was similar to our 'relaxed' group (median four injections, from 12 to 24 months) [15].

In our study, the 'relaxed' outliers had particularly poor control of CST in CRVO for 2 years and poorer visual outcomes compared with the 'typical' and 'intensive' groups. The detrimental effect of the 'relaxed' treatment of BRVO on outcomes seemed less marked than it was in CRVO in our study. This was in keeping with the HORIZON open label extension study (second year of treatment) where participants that had already completed the BRAVO and CRUISE studies were allowed to have reviews extended out to 3 months [14, 16, 19, 26, 27]. There was a generalised loss of vision during that second year, particularly for eyes with CRVO, with few injections being delivered (CRVO: 2.0–3.8 injections, BRVO: 2.0–2.4 injections). The authors concluded that patients with RVO, particularly those with CRVO, were prone a vision loss when reviewed and treated less frequently.

The observation in our study that a similar proportion of eyes achieved VA > 68 letters (approx. 20/40) at some point suggests similar potential for good outcomes across all the groups. How long eyes stayed at that level was what differentiated the groups. Intensively treated eyes had significantly longer 'time-in-range' with VA > 68 letters (BRVO: $p < 0.01$, CRVO: $p = 0.04$). The longer

TABLE 3 | Baseline demographics of BRVO and CRVO eyes treated by the most intensive practitioner compared with the two other intensive practitioners.

	Intensive BRVO (156 eyes)			Intensive CRVO (189 eyes)		
	Most intensive	**Other intensive**	***p*[a]**	**Most intensive**	**Other intensive**	***p*[a]**
Practitioners, *n*	1	2		1	2	
Eyes, *n*	106	55		85	104	
Patients, *n*	105	54		85	102	
Mean interval, weeks (SD)	6.0 (1.9)	6.7 (2.1)	0.05	6.3 (3)	6.9 (2.5)	0.56
VA, letters (SD)	64.3 (15)	58.2 (19.9)	**0.03**	46 (24.1)	38.2 (27.9)	**0.04**
≤35 letters, %	4%	15%	**0.02**	28%	47%	**0.02**
≥70 letters, %	45%	35%	0.24	13%	18%	0.24
CST, μm (SD)	444 (131)	449 (142)	0.85	602 (200)	619 (283)	0.85
Age, years (SD)	69.6 (12)	69.9 (12.7)	0.86	69.6 (12.4)	71.6 (11.8)	0.86
Gender, % female	58%	51%	0.50	39%	47%	0.50
Initial injection						
Bevacizumab, %	100%	18%	**<0.01**[b]	100%	8%	**<0.01**[b]
Ranibizumab, %	—	42%		—	50%	
Aflibercept, %	—	40%		—	42%	

Note: P values < 0.05 (bold) were considered significant.

Abbreviations: BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, CST = central subfield thickness, n = number, SD = standard deviation, VA = visual acuity.

[a]*p*-values were derived using analysis of variance (ANOVA).

[b]Chi-square test on 3 × 3 contingency tables.

time-in-range for the BRVO 'intensive' group comes with one caveat: higher baseline VA ($p < 0.01$) compared with the BRVO 'typical' and 'relaxed' groups. In CRVO particularly, perhaps the current degree of extending treatment intervals in the routine clinical practice results in degradation of the initial VA gains.

The present study graded the treatment frequency of practitioners rather than individual eyes to avoid the potential confounding effect of disease severity. We wanted to maintain the patient samples presenting to each practitioner rather than split them up. We also adjusted for baseline differences and VEGF inhibitor utilisation. The Vestrum Health Database reported a similar range of outcomes based on treatment frequency in RVO (+2.0 to +15.5 letters in CRVO and +2.9 to +13.1 letters in BRVO), but in that study, the eyes treated with increasing frequency had progressively lower baseline VA [1]. The range of gains in VA in the present study adds to the existing evidence; the methodology also likely isolates the effect on outcomes of treatment frequency from disease severity.

This study has some limitations common to observational analyses. We report and discuss the relative benefits of different levels of treatment frequency while not having the power to demonstrate any significant association with the risk of endophthalmitis, though it makes sense to assume the risk would likely be proportional to injection frequency. The range of outcomes using currently available VEGF inhibitors reported here can at least inform the management of patients in keeping with their individual tolerance of risk and treatment burden. Our conclusions are based on the difference in outcomes in eyes treated by only three intensive and four relaxed outliers, compared with 22 typical practitioners; however, the proportion of patients treated by those outliers was quite large. We adjusted for the effect of which the VEGF inhibitor was initiated; however, we did not account for any effect caused by switching VEGF inhibitors. The switching rates were below 20%, similar to other FRB! RVO cohorts, and occurred between the first-generation VEGF inhibitors with which only small differences in visual outcomes have been demonstrated in CRVO only [2, 28]. Neither neovascularisation (combined anterior or posterior) nor rubeosis was found to be significantly associated with injection frequency, though the most intensive practitioner had very low rates of these. We cannot be sure that users fulfilled their agreement to track at least 85% of the patients they managed with the relevant condition. We report some anomalous outcomes such as the rates of macular changes affecting vision during the study in CRVO occurring in around 20% of eyes in 'intensive' and 'relaxed' groups but in only 10% in the 'typical' frequency CRVO group: the higher rates of cataract surgery in the 'relaxed' group and higher rates of laser in the 'intensive' group. We assume that cataract surgery may be more common in physicians with a more general focus. One would think that more frequent cataract surgery may have improved outcomes in the relaxed group. It was interesting that the single most intensive practitioner was responsible for the higher rate of focal laser in the intensive group. There is limited evidence to suggest that focal laser in BRVO can have an adjunctive benefit to visual outcomes or reduce the number

TABLE 4 | Outcomes in BRVO and CRVO eyes treated by the most treatment-intensive practitioner compared with the two other intensive practitioners at 24 months.

	Intensive BRVO (156 eyes)			Intensive CRVO (189 eyes)		
	Most intensive	**Other intensive**	***p***	**Most intensive**	**Other intensive**	***p***
Eyes, *n*	106	55		85	104	
24 m completers, *n* (%)	92 (87%)	41 (75%)	0.08	79 (93%)	75 (72%)	**<0.01**
24 m VA, mean (SD), letters	79 (11)	72 (19)	**<0.01**	66 (22)	51 (29)	**<0.01**
≤35 letters, *n* (%)	1%	7%	0.05	13%	29%	**0.01**
≥70 letters, *n* (%)	83%	75%	0.21	52%	41%	0.19
Gain ≥15 letters, *n* (%)	47%	49%	0.87	61%	42%	**0.01**
Loss ≥15 letters, *n* (%)	1%	2%	1.00	5%	11%	0.18
Δ VA, mean (95% CI), letters	15 (12, 17)	14 (10, 18)	0.68	20 (15, 24)	13 (8, 18)	0.05
24 m CST, mean (SD), μm	275 (47)	282 (72)	0.64	280 (69)	303 (158)	0.89
Δ CST, mean (95% CI), μm	−169 (−196, −142)	−166 (−211, −121)	0.93	−322 (−368, −275)	−316 (−374, −258)	0.90
Injections, median (Q1, Q3)[a]	20 (15, 25)	16 (12, 19)	**<0.01**	21 (14, 25)	15 (12, 19)	**<0.01**
Final interval, median (Q1, Q3) weeks[a]	6 (4, 10)	8 (6, 9)	0.26	6 (4, 10)	6 (4, 10)	0.67
Visits, median (Q1, Q3)[a]	22 (17, 27)	21 (18, 25)	0.68	22 (17, 26)	22 (19, 27)	0.16
Visits with injections, %	88%	70%	**<0.01**	87%	66%	**<0.01**
Time-in-range (TIR)[b]						
Achieved VA > 68 letters, %	91%	80%	0.13	71%	65%	0.36
TIR, weeks, mean (% weeks)	90 (86%)	90 (88%)	0.97	74 (72%)	63 (60%)	**0.04**
Switched VEGF inhibitor, *n* (%)	17 (16%)	17 (31%)	**0.04**	15 (18%)	26 (25%)	0.29

Note: P values < 0.05 (bold) were considered significant.

Abbreviations: CI = confidence interval, CST = central subfield thickness, *n* = number, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, VA = visual acuity, VEGF = vascular endothelial growth factor.

[a]Calculated in 24-month completers.

[b]Includes completers that achieved > 68 letters within the study duration, mean time expressed in weeks and as a mean percentage of the 104-week study.

of injections required in eyes already receiving VEGF inhibitors [29–31]. Because of anonymisation of data, we can offer no further insight into how the most intensive practitioner achieved such high completion rates despite what appeared to be a very high burden of therapy. Perhaps, newer agents will offer greater durability to offset the sub-optimal levels of disease control seen anatomically in many of the CRVO eyes treated with either 'typical' or 'relaxed' intensity while also reducing the sheer number of injections required to achieve optimal outcomes seen in the 'intensive' groups with either BRVO or CRVO in our study [32].

We found a strong association between treatment frequency and outcomes of VEGF inhibition in RVO at 24 months by benchmarking practitioners with a funnel plot. Our findings suggest

that very frequent treatment in RVO can achieve outcomes matching VEGF trial results in the real-world setting while also highlighting the pervasiveness of undertreatment, even perhaps in doctors with 'typical' levels of treatment intensity. When selecting a treatment regimen, it should balance the individual expectations of patients in keeping with their tolerance of risk and treatment burden.

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Conflicts of Interest

M.G. and D.B. are the inventors of the software used to collect the data for this analysis. The following authors are members of the advisory boards of Novartis and Bayer (P.-H.G., L.O.T., T.P. and M.G.), Roche (A.H., M.G. and T.P.), Allergan (P.-H.G. and M.G.), and Horus and Zeiss (P.-H.G.). Honoraria were reported from Bayer and Novartis (P.-H.G. and L.O.T.); travel expenses were from Novartis, Bayer and Roche (L.O.T. and A.H.); D.B. received a research grant from Novartis.

Data Availability Statement

Research data are not shared.

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ARTICLE OPEN

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Changes in 12-month outcomes over time for age-related macular degeneration, diabetic macular oedema and retinal vein occlusion

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OBJECTIVES: To identify whether the outcomes of neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DMO) and retinal vein occlusion (RVO) in routine clinical practice have changed over time.
METHODS: We analysed 12-month outcomes in treatment-naïve eyes that started aflibercept or ranibizumab for nAMD (3802 eyes), DMO (975 eyes), Branch RVO (BRVO, 357 eyes), Central RVO (CRVO, 371 eyes) and Hemi-RVO (HRVO, 54 eyes) from 2015 and 2019 tracked in the prospectively designed observational Fight Retinal Blindness! Registry.
RESULTS: The mean VA change at 12-month for each year between 2015 and 2019 remained stable or otherwise showed no discernible trends over time in eyes with nAMD (+3.3 to +6 letters), DMO (+3.6 to +6.7 letters) and RVO (+10.3 to +11.7 letters for BRVO, +5.9 to +17.7 letters for CRVO and 10.2 to 20.7 letters for HRVO). The median number of VEGF-inhibitor injections in eyes that completed 12-month follow-up also remained stable at 8–9 for nAMD, 6–7 for DMO, 7–9 for RVO. Fewer eyes (<one-fourth) that started treatment between 2015 and 2018 and more eyes starting in 2019 did not complete 12-month's follow-up visit. The mean VA in non-completers at their last visit was higher than that of their baseline visit.
CONCLUSIONS: Treatment patterns and outcomes for nAMD, DMO and RVO in routine clinical practice have stabilised over the past 5 years at levels inferior to those reported by the pivotal phase 3 studies. A conscious effort to treat these conditions more intensively, or with longer lasting agents, would likely improve outcomes further in our patients.

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INTRODUCTION

Vascular endothelial growth factor (VEGF) inhibitors have been the first-line treatment of neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DMO) and retinal vein occlusion (RVO) since their efficacy was first established in the pivotal clinical trials [1–3]. Studies reported that eyes with nAMD, DMO and RVO received fewer VEGF-inhibitor treatments in routine clinical practice, with inferior outcomes, than those in the clinical trials [4–17]. An earlier analysis from the Fight Retinal Blindness! Registry reported that the 2-year visual outcomes of nAMD in routine clinical practice improved from +2.7 letters for eyes starting treatment in 2007 to +7.8 letters for those starting in 2012 as injection rates over two years increased from 10 in 2007 to 14 in 2012 [18, 19]. The outcomes in eyes that started VEGF inhibitors for DMO in routine clinical practice improved after 2013 because the treatment was started earlier when the visual acuity was better and injections were more frequent than those that started in the previous years [10–12]. Data on more recent outcomes may establish whether treatments have improved further over time and identify areas where they appear suboptimal if they have not. This study aimed to report 12-month outcomes in eyes that started VEGF inhibitors for nAMD, DMO and RVO from 2015 to 2019 in routine clinical practice.

METHODS

Design, data sources and measurements

Data were collected in the prospectively designed web-based registry for tracking treatment outcomes of macular diseases—The Fight Retinal Blindness (FRB)! Registry [20]. The registry has modules to collect data of eyes that receive treatment for nAMD, DMO and RVO in routine clinical practice.

The data recorded at each clinical visit include the number of letters read on a logarithm of the minimum angle of resolution (logMAR) VA Chart, the activity of the choroidal neovascular membrane (CNV) in eyes with AMD and central subfield thickness (CST [μm]) for DMO and RVO assessed using spectral-domain optical coherence tomography (OCT),

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procedures and ocular adverse events. Enrolment in the audit required a baseline visit when the first injection was administered that had extra data points regarding demographics, type (AMD, diabetes, RVO) and the presence or absence of key risk factors. All treatment decisions, including choice of treatment and frequency of visits, were based on VA and OCT at the discretion of the practitioner in consultation with the patient, thereby reflecting real-world clinical practice.

Participants in this analysis were patients from practices in Australia, France, Italy, Switzerland and the United Kingdom. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the Southeastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (Société Française d'Ophtalmologie Institutional Review Board), the Ethics Committee of the University of Milan, the Cantonal Ethics Committee Zurich and the Caldicott Guardian at the Royal Free London NHS Foundation Trust. Informed consent ('opt-in consent') was sought from patients in France, Italy and Switzerland. Ethics committees in Australia approved the use of "opt-out" patient consent. Data in the registry are anonymized and compliant with the UK Policy Framework for Health and Social Care Research. This study adhered to the tenets of the Declaration of Helsinki.

Patient selection

Treatment naïve eyes that started ranibizumab (0.5 mg Lucentis; Genentech, Inc., South San Francisco, CA; Novartis, Basel, Switzerland) or aflibercept (2 mg Regeneron Pharmaceuticals Inc., Tarrytown, NY/Bayer, Leverkusen, Germany) for the treatment of nAMD, DMO and RVO from 1 January 2015 to 31 December 2019 allowing the possibility of having at least 12 months of follow-up. Eyes that received fewer than 2 injections were excluded from the analysis. Eyes that completed at least 12 months of visits were defined as 'completers'. Eyes that did not complete 12 months of observations were defined as 'non-completers'.

Outcomes

The main outcome was the mean change in VA at 12 months for each year from 2015 to 2019. Secondary outcomes were the number of injections and visits over 12 months for each year, the proportion of visits that were graded active each year in eyes with nAMD, mean change in CST at 12 months for each year in eyes with DMO and RVO, the proportion of eyes with VA ≥ 69 letters (Snellen equivalent 20/40) and ≤35 letters (20/200) at baseline and 12 months for each year and the proportion of eyes that gained ≥10 letters and those that lost ≥10 letters at 12 months for each year. Other outcomes of interest were the non-completion rates for each year.

Statistical analysis

Descriptive data included the mean (standard deviation), median (first and third quartiles) and percentages where appropriate. Eyes were considered to have been observed from the first treatment visit up to their 12 months (365 ± 30 days) visit. Paired *t* tests, Wilcoxon signed-rank test, Chi-square and Fisher tests were used as appropriate to compare the changes at 12 months from the baseline. Line graphs were used to visualise changes in VA and CST and bar plots for the number of injections and visits at 12 months.

We used mixed-effects models to compare VA outcomes at 12 months over time. The models were adjusted for age, baseline CST (for DMO and RVO), baseline VA, (fixed-effects), and practice and intra-patient correlation for bilateral cases (random-effects) with year of treatment initiation as a continuous variable. All analysis will be conducted using R statistical software version 4.1.2 (http://www.R-project.org/) with the *glmmTMB* package (V1.1.2.3) for multivariate analysis [21].

RESULTS

Study participants

A total of 3802 eyes (3284 patients) with nAMD, 975 eyes (718 patients) with DMO, 357 eyes (351 patients) with branch retinal vein occlusion (BRVO), 371 eyes (368 patients) with central retinal vein occlusion (CRVO) and 54 eyes (54 patients) with Hemi-retinal vein occlusion (HRVO) started VEGF inhibitors whose treatment outcomes were tracked in the registry in the period specified. Data from both eyes of 518 nAMD, 257 DMO, 6 BRVO and 3 CRVO patients were included in the analysis. Table 1 summarises the baseline characteristics of these eyes. The baseline characteristics of eyes for each year from 2015 to 2019 in the disease group of nAMD, DMO, BRVO, CRVO and HRVO are reported in Supplementary Table 1.

Visual outcomes at 12 months in completers

Figure 1A illustrates the mean VA at baseline and 12 months, and the mean change in VA over 12 months in eyes with nAMD stratified by the year of starting VEGF-inhibitor treatment. The mean VA at baseline, 59.4–62.9 letters (Snellen equivalent: 20/63–20/60), and the mean gain in VA at 12 months, 3.3–6 letters ($p = 0.38$), for each treatment year tended to be similar (Table 2). The mean VA 12 months after starting treatment was 64–66 letters (Snellen equivalent: 20/50). The proportion of eyes with VA ≥ 69 letters increased (54–60% at 12 months from 41–47% at baseline). Around 27–35% of eyes gained ≥ 10 letters over 12 months (Table 2).

Table 1. Demographic characteristics.

	nAMD	DMO	BRVO	HRVO	CRVO
Eyes, *n*	3802	975	357	54	371
Patients, *n*	3284	718	351	54	368
Female, *n* (%)	2012 (61)	259 (36)	185 (53)	23 (43)	167 (45)
Right Eye, *n* (%)	1957 (52)	501 (51)	195 (55)	24 (44)	194 (52)
Age years, mean (SD)	80 (9)	63 (12)	71 (12)	73 (11)	72 (13)
Baseline VA letters, mean (SD)	59.2 (20)	65.4 (16.8)	58 (18)	47.9 (23.9)	42 (26)
VA ≥ 69 letters, %	41	56	33	26	17
VA ≤ 35 Less, %	14	7	12	32	39
CST, µm (SD)	–	415 (126)	472 (156)	576 (212)	624 (229)
Lesion, %	CNV lesion type	DMO type	Ischaemia	Ischaemia	Ischaemia, %
	Type 1—41 Type 2—17 Type 3—5 Other—5 Not done—32	Centre-involving—88 Non centre-involving—9 No CSME—3	Macular—5 Peripheral—13	Macular—4 Peripheral—30	Macular—6 Peripheral—21

nAMD Neovascular age-related macular degeneration, *DMO* Diabetic macular oedema, *BRVO* Branch retinal vein occlusion, *HRVO* Hemi-retinal vein occlusion, *CRVO* Central retinal vein occlusion, *n* number, *SD* standard deviation, *DR* Diabetic retinopathy, *VA* visual Acuity, *CST* Central subfield thickness, *CNV* Choroidal neovascularization.

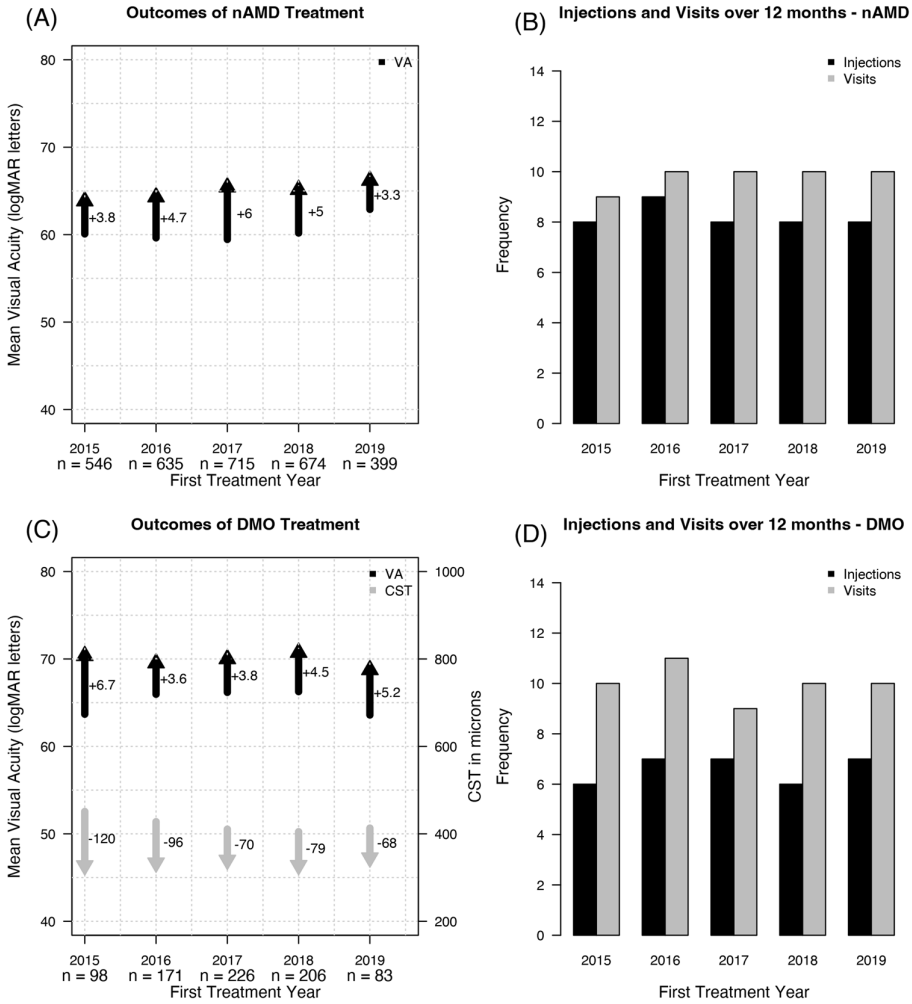

Fig. 1 Treatment outcomes in age-related macular degeneration and diabetic macular oedema. A Mean change in visual acuity (VA) at 12 months in eyes that completed 12 months of vascular endothelial growth factor (VEGF) inhibitor treatments for neovascular age-related macular degeneration (nAMD). Outcomes are shown by the year of treatment initiation. The base of each arrow represents the mean baseline VA while the point represents the mean final VA. The mean changes in VA are reported next to the arrows. '*n*' represents number of eyes. **B** Bar plot illustrates the median number of VEGF-inhibitor treatments (black bar) and visits (grey bar) over 12 months. **C** Mean change in visual acuity (VA, black) and central subfield thickness (CST, grey) at in eyes that completed 12 months of vascular endothelial growth factor (VEGF) inhibitor treatments for diabetic macular oedema (DMO). Outcomes are shown by the year of treatment initiation. The base of each arrow represents the mean value at baseline while the point represents the mean value at 12 months. The mean changes are reported next to the arrows. '*n*' represents number of eyes. **D** Bar plot illustrates the median number of VEGF-inhibitor treatments (black bar) and visits (grey bar) over 12 months.

Eyes with DMO tended to have a similar mean change in VA (+3.6 to +6.7 letters, $p = 0.48$) at 12 months from a similar mean VA at baseline of 63.6–66.3 letters (Snellen equivalent: 20/50) when they started treatment (Fig. 1C, Table 2). The mean VA at 12 months from the start of treatment for each year was 69–71 letters (Snellen equivalent: 20/40). More than three-fourths (60–71%) eyes achieved VA ≥ 69 letters over 12 months (Table 2). Almost a quarter to one-third (24–37%) eyes gained ≥10 letters at 12 months (Table 2).

The mean change in VA at 12 months in eyes with BRVO that started VEGF inhibitors in 2015 to 2019 is illustrated in Fig. 2A. The mean change in VA at 12 months was +10.3 to +11.7 letters from a similar mean VA at baseline of 56.7–63.5 letters (Snellen equivalent: 20/70–20/60, $p = 0.96$, Table 2). The mean VA at 12 months from the start of VEGF-inhibitor treatment was 68–74 letters (Snellen equivalent: 20/40, Table 2). The proportion of eyes with VA ≥ 69 letters at 12 months increased (58–79%). More than 50% of eyes gained 10 or more letters (Table 2).

Figure 2B shows the mean change in VA at 12 months in eyes that started VEGF inhibitors for CRVO. The mean VA change in CRVO eyes ranged from +5.9 to +17.7 letters from the mean VA of 36–45.3 letters (Snellen equivalent: 20/200–20/125) at baseline (Table 2). The proportion of eyes with VA ≥ 69 letters at 12 months increased from the baseline while those with VA ≤ 35 letters decreased (Table 2). The mean VA at 12 months improved to 45.5–63 letters (Snellen equivalent: 20/160–20/63; $p = 0.98$, Table 2).

Eyes with HRVO at baseline had a similar trend to those of CRVO eyes (Table 1, Supplementary Table 1). The mean VA change at 12 months in eyes with HRVO was +10.2 to +20.7 letters from a mean VA of 47.1–54.5 letters (Snellen equivalent: 20/125–20/80), $p = 0.96$, at baseline (Table 2). The proportion of

Table 2. Outcomes in completers stratified by year of starting treatment.

	2015	2016	2017	2018	2019
Age-related macular degeneration					
Completers, *n* (%)	546 (84)	635 (79)	715 (87)	674 (75)	399 (63)
Patients, *n*	512	591	662	612	369
Baseline VA letters, mean (SD)	60.1 (18.7)	59.6 (19.4)	59.4 (20.5)	60.2 (20.4)	62.9 (17.5)
Final VA letters, mean (SD)	63.8 (19.2)	64.3 (20.7)	65.4 (19.9)	65.1 (19.7)	66.2 (18.6)
Change VA letters, mean (95% CI)[a]	3.8 (2.5, 5)	4.7 (3.4, 5.9)	6 (4.9, 7.1)	5 (3.8, 6.1)	3.3 (1.8, 4.8)
Gain ≥10 letters %	31	32	35	31	27
Loss ≥10 letters %	13	12	10	11	12
VA ≥ 69 letters %, baseline/final	41/54	41/59	43/59	44/61	47/60
VA ≤ 35 letters %, baseline/final	12/11	12/12	13/9	13/11	10/8
Injections, median (Q1, Q3)	8 (7, 10)	9 (7, 10)	8 (6, 10)	8 (6, 10)	8 (7, 10)
Visits, median (Q1, Q3)	9 (8, 12)	10 (8, 12)	10 (8, 12)	10 (8, 12)	10 (8, 12)
Active CNV visits, %	36	31	31	24	18
Diabetic macular oedema					
Completers, *n* (%)	98 (94)	171 (89)	226 (88)	206 (75)	83 (56)
Patients, *n*	78	133	185	157	63
Baseline VA letters, mean (SD)	63.7 (17.5)	66 (15.8)	66.2 (17.3)	66.3 (16.8)	63.6 (16.7)
Final VA letters, mean (SD)	70.4 (14)	69.5 (16.2)	70 (14.6)	70.7 (17.6)	68.8 (15.8)
Change VA letters, mean (95% CI)[b]	6.7 (3.3, 10.1)	3.6 (1.6, 5.5)	3.8 (2, 5.7)	4.5 (2.6, 6.3)	5.2 (2.1, 8.2)
Gain ≥10 letters %	33	30	24	27	37
Loss ≥10 letters %	7	12	12	7	8
VA ≥ 69 letters %, baseline/final	42/60	53/67	54/66	58/71	53/71
VA ≤ 35 letters %, baseline/final	7/2	5/4	6/3	7/6	7/4
Baseline CST μm, mean (SD)	451 (149)	428 (129)	411 (125)	405 (125)	413 (115)
Final CST μm, mean (SD)	327 (91)	334 (102)	340 (103)	328 (97)	345 (106)
Change CST μm, mean (95% CI)	−120 (−152, −88)	−96 (−116, −77)	−70 (−86, −53)	−79 (−95, −62)	−68 (−92, −44)
Injections, median (Q1, Q3)	6 (4, 8)	7 (5, 9)	7 (5, 8)	6 (4, 9)	7 (5, 9.5)
Additional laser, *n*	7	3	6	2	3
Additional Triamcinolone, *n*	1	1	2	0	0
Additional Ozurdex®, *n*	6	11	5	9	8
Visits, median (Q1, Q3)	10 (8, 12)	11 (8, 14)	9 (7, 12)	10 (7.2, 13)	10 (8, 14)
Branch retinal vein occlusion					
Completers, *n* (%)	37 (90)	76 (93)	73 (88)	73 (79)	38 (66)
Patients, *n*	37	76	72	73	36
Baseline VA letters, mean (SD)	58.8 (17.9)	56.7 (18.4)	59.9 (16.8)	57.3 (19.2)	63.5 (17)
Final VA letters, mean (SD)	70.5 (14)	67.5 (16.9)	71 (17.6)	69 (17.2)	73.8 (16.3)
Change VA letters, mean (95% CI)[c]	11.7 (5.7, 17.7)	10.8 (7, 14.6)	11.1 (7.4, 14.8)	11.7 (7.5, 15.9)	10.3 (6.2, 14.4)
Gain ≥10 letters %	51	51	59	52	53
Loss ≥10 letters %	8	8	7	9	5
VA ≥ 69 letters %, baseline/final	30/62	29/58	29/75	36/67	47/79
VA ≤ 35 letters %, baseline/final	11/5	12/4	7/4	19/7	5/3
Baseline CST μm, mean (SD)	450 (155)	483 (148)	469 (152)	469 (166)	452 (149)
Final CST μm, mean (SD)	343 (115)	331 (111)	315 (104)	313 (111)	323 (101)
Change CST μm, mean (95% CI)	−108 (−173, −43)	−155 (−195, −115)	−155 (−198, −113)	−156 (−200, −112)	−129 (−182, −75)
Injections, median (Q1, Q3)	7 (5, 9)	8 (5, 9)	7 (5, 9)	7 (6, 9)	8 (6, 8)
Additional macular laser, *n*	2	3	3	1	0
Additional PRP laser, *n*	8	18	6	16	4
Additional Ozurdex®, *n*	3	2	2	1	2
Visits, median (Q1, Q3)	9 (8, 11)	10 (8, 11)	10 (8, 11)	10 (8, 12)	9 (8, 11)
Central retinal vein occlusion					
Completers, *n* (%)	42 (96)	76 (85)	67 (83)	78 (79)	28 (51)
Patients, *n*	42	75	66	78	28
Baseline VA letters, mean (SD)	40.7 (24)	36 (27.7)	49 (22.4)	45.3 (26.6)	39.7 (28.1)
Final VA letters, mean (SD)	58.5 (25.4)	46.5 (29.8)	63 (22.2)	55.4 (27.2)	45.5 (31.9)
Change VA letters, mean (95% CI)[d]	17.7 (9.2, 26.3)	10.6 (4.7, 16.4)	13.9 (8.3, 19.5)	10.1 (3.4, 16.8)	5.9 (−5.1, 16.8)
Gain ≥10 letters %	71	50	69	44	36
Loss ≥10 letters %	10	15	15	13	25
VA ≥ 69 letters %, baseline/final	14/41	12/30	15/54	24/40	21/32

Table 2. continued

	2015	2016	2017	2018	2019
VA ≤ 35 letters %, baseline/final	45/17	46/37	24/13	35/24	42.9/36
Baseline CST µm, mean (SD)	609 (209)	618 (265)	631 (205)	622 (251)	634 (227)
Final CST µm, mean (SD)	352 (201)	343 (200)	359 (168)	342 (202)	367 (221)
Change CST µm, mean (95% CI)	−260 (−350, −171)	−274 (−348, −201)	−277 (−342, −211)	−290 (−359, −222)	−241 (−368, −114)
Injections, median (Q1, Q3)	8 (6, 10)	7 (5, 9)	8 (6, 10)	8 (5, 10)	9 (7, 9)
Additional macular laser, *n*	0	0	1	0	0
Additional PRP laser, *n*	7	24	14	22	11
Additional Ozurdex®, *n*	1	2	3	6	1
Visits, median (Q1, Q3)	10 (9, 13)	11 (9, 13.2)	10 (8, 13)	11 (8, 13)	11 (9, 13)
Hemi-retinal vein occlusion					
Completers, *n* (%)	6 (100)	7 (78)	15 (75)	12 (86)	4 (80)
Patients, *n*	6	7	15	12	4
Baseline VA letters, mean (SD)	54.5 (14.4)	47.1 (29.1)	53.6 (21.4)	47.9 (27.1)	48.8 (12.5)
Final VA letters, mean (SD)	73.2 (10.2)	61.4 (29.4)	68.7 (12.1)	68.6 (15.8)	59 (27.4)
Change VA letters, mean (95% CI)[e]	18.7 (−0.8, 38)	14.3 (−5.2, 33.8)	15.1 (4.7, 25.5)	20.7 (10.1, 31.3)	10.2 (−15.3, 35.8)
Gain ≥10 letters %	83	71	60	61	50
Loss ≥10 letters %	17	14	7	0	25
VA ≥ 69 letters %, baseline/final	17/83	43/43	27/60	33/58	0/50
VA ≤ 35 letters %, baseline/final	17/0	43/14	27/0	25/0	25/25
Baseline CST µm, mean (SD)	700 (71)	616 (263)	477 (187)	532 (167)	663 (203)
Final CST µm, mean (SD)	395 (258)	318 (88)	298 (121)	329 (127)	355 (144)
Change CST µm, mean (95% CI)	−305 (−587, −22)	−298 (−535, −61)	−179 (−291, −67)	−203 (−327, −79)	−308 (−706, 90)
Injections, median (Q1, Q3)	10 (8, 10)	8 (7, 10)	7 (5, 9)	7 (6, 9)	9 (8, 9)
Additional macular laser, *n*	0	0	1	0	0
Additional PRP laser, *n*	1	6	7	3	0
Additional Ozurdex®, *n*	0	1	0	0	0
Visits, median (Q1, Q3)	10 (9, 11)	12 (10, 13)	9 (8, 13)	9 (9, 11)	9 (8, 10)

We used mixed-effects models to compare VA outcomes at 12 months over time. The models were adjusted for age, baseline CST (for DMO and RVO), baseline VA, (fixed-effects), and practice and intra-patient correlation for bilateral cases (random-effects) with year of treatment initiation as a continuous variable.
n Number, *VA* Visual Acuity, *SD* Standard Deviation, *CI* Confidence Interval, *CST* Central Subfield Thickness, *Q1* First Quantile, *Q3* Third Quantile, *PRP* Panretinal photocoagulation.
[a]$p = 0.38$.
[b]$p = 0.48$.
[c]$p = 0.96$.
[d]$p = 0.98$.
[e]$p = 0.96$.

eyes with VA ≥ 69 letters at 12 months ranged from 43–80% while those with VA ≤ 35 letters was less than a quarter (Table 2).

Macular thickness

There were no consistent trends in the mean CST reductions (−120 to −68 µm) at 12 months from the baseline (mean CST: 405–451 µm) or the mean CST at 12 months (327–345 µm) from 2015–2019 in eyes with DMO (Table 2, Fig. 1C).

Eyes with RVO tended to have a stable CST outcome between 2015 and 2019 with a mean CST change (−156 to −108 µm for BRVO, −290 to −241 µm for CRVO and −308 to −179 µm for HRVO) at 12 months from the start of VEGF-inhibitor treatment for each year from the baseline CST (mean CST: 450–483 µm for BRVO, 342–367 µm for CRVO and 298–395 for HRVO; Fig. 2 and Table 2).

Treatments and visits

The median number of VEGF-inhibitor injections for nAMD in eyes completing 12-month observation from the start of treatment for each year appeared to be stable with a median of 8–9 injections from a median of 9–10 visits (Fig. 1B, Table 2). Similarly, eyes with DMO received a median of 6–7 VEGF-inhibitor injections over the 12 months from a median of 9–11 visits (Fig. 1D) with no clear trends indicating an increase in the number of injections over time. A few eyes in each treatment year required additional treatments, macular laser sessions and intravitreal steroid injections (triamcinolone and Ozurdex® [Allergan Inc., Irvine, CA], Table 2). The number of VEGF-inhibitor treatments in eyes with RVO tended to be similar each year with a median injection of 7–8 injections from a median of 9–10 visits for BRVO (Fig. 2B), 7–9 injections from 10 to 11 visits for CRVO (Fig. 2C) and 7–10 injections from 9 to 12 visits for HRVO (Fig. 2F). A few eyes with RVO required additional treatments, laser (macular, sectoral) and steroid injections (triamcinolone, Ozurdex®), over 12 months (Table 2).

Activity of lesions

The proportion of visits when eyes with nAMD that completed 12-month visit was graded as active tended to decrease over time from 36% of eyes starting treatment in 2015 to 18% in 2019 (Table 2).

Non-completion rate at 12 months

Almost a quarter of eyes that started VEGF inhibitor for nAMD during 2015–2018 and a slightly larger proportion (37%) in 2019 did not complete 12 months of observations (Fig. 3A). The mean VA in these eyes at their last visit was better than at the start of treatment and the mean change in VA at dropout for each treatment start year tended to be similar, +2.5 to + 4.2 letters (Fig. 3A).

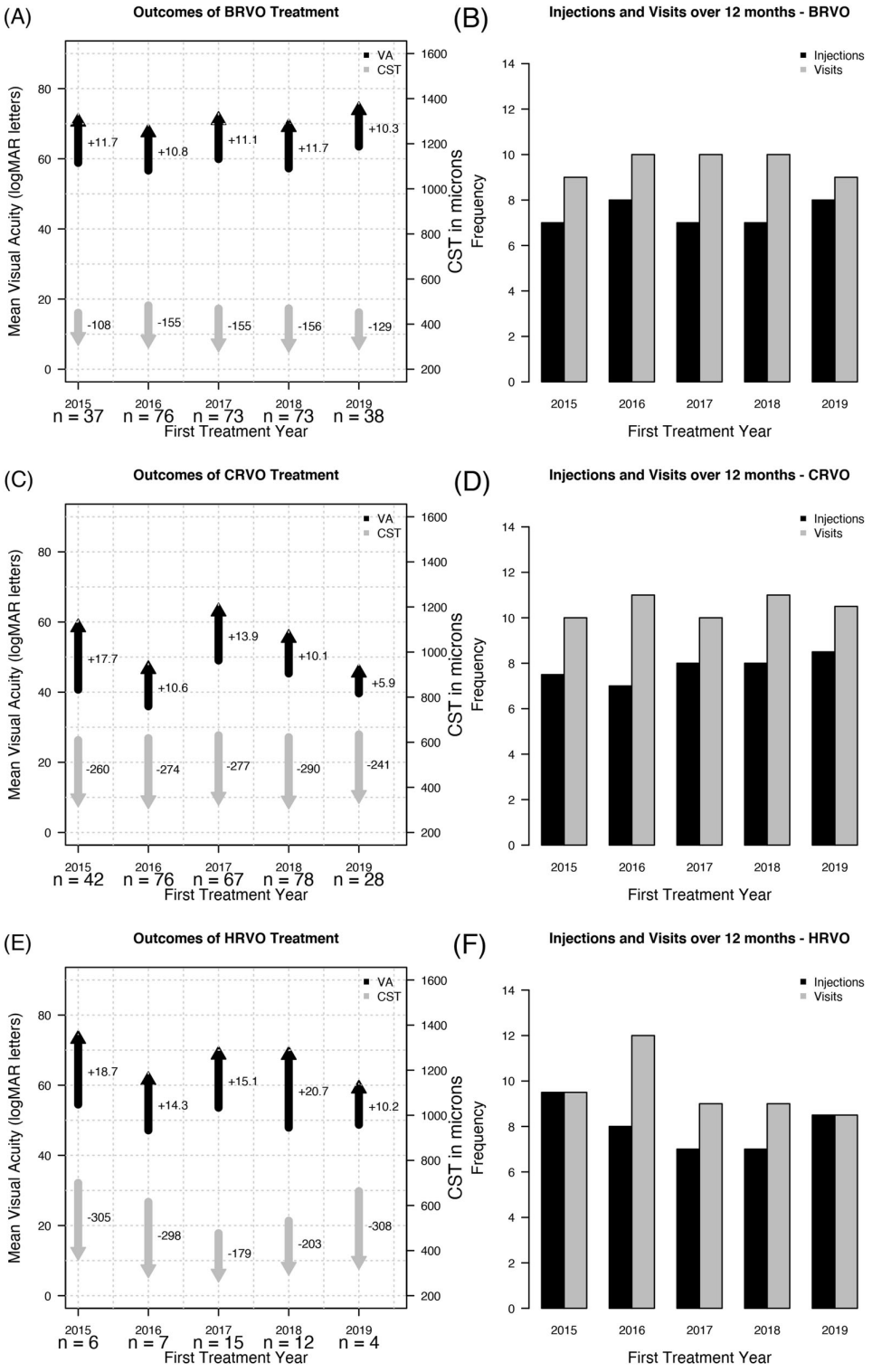

Fig. 2 Treatment outcomes in retinal vein occlusion. Mean change in visual acuity (VA, black) and central subfield thickness (CST, grey) in eyes that completed 12 months of vascular endothelial growth factor (VEGF) inhibitor treatments for branch retinal vein occlusion (BRVO, **A**), central retinal vein occlusion (CRVO, **C**) and hemi-retinal vein occlusion (HRVO, **E**). Outcomes are shown by the year of treatment initiation. The base of each arrow represents the mean value at baseline while the point represents the mean value at 12 months. The mean changes are reported next to the arrows. Bar plot illustrates the median number of VEGF-inhibitor treatments (black bar) and visits (grey bar) over 12 months for the BRVO (**B**), CRVO (**D**) and HRVO (**F**) cohorts.

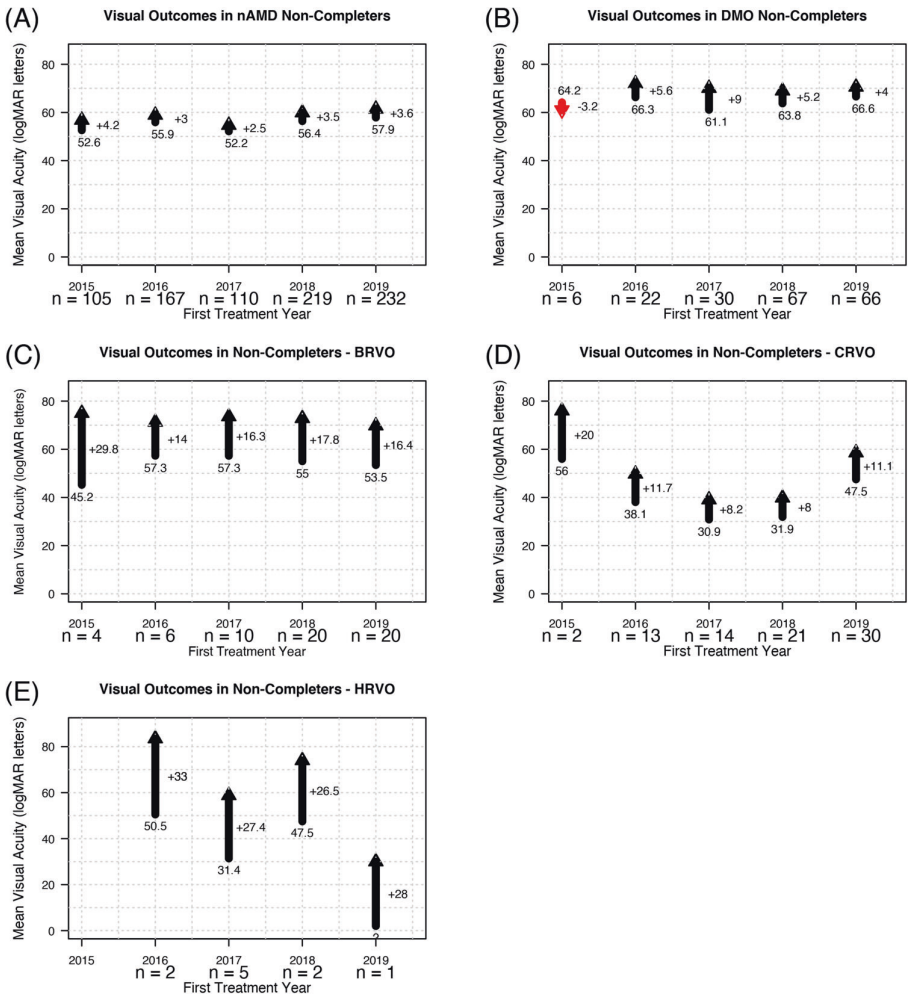

Fig. 3 Outcomes in non-completers. Mean change in visual acuity in non-completers from baseline (base) to their last observed visit (point) in eyes that started vascular endothelial growth factor (VEGF) inhibitor treatments for (**A**) neovascular age-related macular degeneration (nAMD), (**B**) diabetic macular oedema (DMO), (**C**) Branch retinal vein occlusion (BRVO), (**D**) Central retinal vein occlusion (CRVO) and (**E**) Hemi-retinal vein occlusion (HRVO). Outcomes are shown by the year of treatment initiation.

Six eyes (6%) that started VEGF inhibitor for DMO in 2015 were lost to follow-up before completing 12 months of observations after losing a mean of 3.2 letters from a mean baseline VA of 64.2 letters (Fig. 3B). Fewer than quarter eyes that started DMO treatment in 2016–2018 were lost before the 12-month visit while the non-completers in 2019 increased to 44% (Table 2). These eyes at their last visit had a mean VA change of +4 to +9 letters from 61.1 to 66.3 letters mean VA at baseline (Fig. 3B). Their mean VA at their last visit was >69 letters (20/40) (Fig. 3B).

Fewer than 20% of eyes that started VEGF inhibitors for BRVO and CRVO between 2015 and 2018 were lost over the first 12 months of treatment. Almost half (44% for BRVO and 49% for CRVO) of those that started treatment in 2019 were lost before completing 12 month's visits. Less than a quarter of eyes with HRVO were lost before 12-month visit (Table 2). The mean change in VA at the last visit from baseline in BRVO non-completers was +14 to +30 letters and their mean VA at the last visit was >69 letters (Fig. 3C). Non-completers in the CRVO group had a mean VA change of +8 to +20 letters at the last visit from the baseline (Fig. 3D) while those in the HRVO gained a mean of 26.5–33 letters (Fig. 3E). The mean VA at the last visit in the CRVO and HRVO non-completers was better than at the start of their treatment.

DISCUSSION

This analysis of data from routine clinical practice that were collected by a prospectively designed registry for tracking treatment outcomes of macular diseases found that the yearly outcomes of nAMD, DMO and RVO that started VEGF inhibitors between 2015 and 2019 were reasonably good. The visual acuity at baseline for all retinal conditions remained static and the mean visual and anatomical outcomes at 12 months only varied slightly across the years but otherwise did not show any noticeable trends, although the level of CNV activity in eyes with nAMD did decrease over time. The number of injections over 12 months did not increase but remained steady at 8–9 injections for nAMD, 6–7 for DMO, and 7–8 for RVO. These data indicate that the 12-month outcomes of nAMD, DMO and RVO in routine clinical practice have stabilised over the past 5 years despite still being inferior to the outcomes reported by the pivotal clinical trials.

Previous observational studies that evaluated the outcomes of VEGF inhibitors for nAMD found that the visual outcomes in routine clinical practice were inferior to those of the clinical trials with fewer treatments [4, 5, 22, 23]. A study from the FRB! Registry found that the treatment frequency for nAMD in routine clinical practice increased from 2007 to 2012 which resulted in an

improvement in the mean change in VA over time [19]. Eyes that started VEGF inhibitors for nAMD in another study of routine clinical practice during 2014 gained a mean of 3.7–4.2 letters at 12 months from a mean of 59 letters at baseline after a mean of 8 VEGF-inhibitor treatments [24]. Studies from the FRB! DMO Registry found that eyes that started treatment from 2009 to 2012 achieved lower 12-month mean VA gains (+2.3 letters from 66 letters at baseline) from fewer treatments (median of 4 injections over 12 months) than those that started treatment after 2013 (+3.1 to +5.4 letters from 64.7–67.8 letters at baseline, median of 6 injections) [10–12]. The present study provides evidence that the treatment outcomes have not impoved further since then and are still inferior to those of clinical trials in which selected patients are managed under a strict protocol regimen.

Eyes presenting with better VA tend to have lower VA gains but are more likely to achieve better vision with treatment [10, 25]. The mean VA at baseline in eyes with nAMD (59 letters), DMO (65 letters) and BRVO (58 letters) in the present study was higher than in those eyes that received VEGF inhibitors in their registrational trials [22, 23, 26–30]. The mean VA at 12 months and the proportion of eyes with VA ≥ 20/40 at 12 months in the present study were similar to those of the registrational trials suggesting that the lower gains in the present study may be the result, in part, of the better starting VA. The mean VA at baseline in eyes with CRVO in the present study was lower, macula thinner and the patients were older than those in clinical trials of VEGF inhibitors for the treatment of CRVO [31–33]. These difference in the baseline characteristics likely contributed to the inferior gains in the present study than those in clinical trials.

The observation that outcomes have remained stable in the last five years might indicate a ceiling may have been reached in what can be achieved in routine clinical practice, which remains inferior to the outcomes of clinical trials. Observational studies may produce results that are inferior to randomised clinical trials due to the biases that are an intrinsic part of the latter [34]. The strict inclusion criteria to be eligible for clinical trials may artificially inflate outcomes by excluding patients that are more likely to have a poor response such as those with comorbidities or more severe disease. Patient compliance and adherence to strict regimens are also more difficult to achieve in routine clinical practice resulting in fewer injections and subsequently worse outcomes.

The limitations of this study are inherent to those of observational studies. Treatment decisions in routine clinical practice, in contrast to those in the clinical trials, are not adjudicated by a reference centre or guided by study protocols. Selection of cases, treatment regimen and follow-up schedule may also differ from clinical trials and among physicians. Treatment regimen for each of the retinal diseases used by the centres/physicians in this study was not recorded in the registry. We found 21% of eyes that started VEGF inhibitors between 2015–2019 for all retinal diseases were lost to follow-up before the 12 month's visit, with increased attrition in eyes starting treatment in 2019 which were definitely affected by COVID-19 pandemic. The mean visual acuity at their last observed visit, except in a few DMO eyes that started treatment in 2015, was better than their baseline which suggests that these eyes could have been lost to follow-up for reasons other than poor outcomes. Nevertheless, we have reported the treatment outcomes of VEGF inhibitors for nAMD, DMO and RVO as they are used in routine clinical practice. There is evidence that carefully designed observational studies, such as the present study, do not consistently overestimate the effectiveness of therapeutic agent [35].

Observational studies may be affected by poor data quality. A recent study of real-world outcomes of nAMD from the American Academy of Ophthalmology Intelligent Research in Sight Registry reported that 35% of VEGF-inhibitor treated eyes recorded in the database lacked baseline and 12-month VA data [36]. The FRB! Registry data can only be accepted into the database for analysis after they have been 'finalised' which starts a built-in validation process that checks whether all mandatory fields have been completed and the values are within the pre-determined ranges, for example, visual acuity has to be between 0 and 100 letters [20]. The data were available for subsequent analysis and reporting only when the visits were finalised [20].

This study found that treatment outcomes of nAMD, DMO and RVO in routine clinical practice with VEGF inhibitors have stabilised in the last 5 years. The outcomes we observed were reasonably good, but treatment frequency, 8–9 injections for nAMD, 6–7 for DMO and 7–8 for BRVO, has stabilised at a rate that is lower to those of their registrational clinical trials,12 for nAMD [22, 23], 8–12 for DMO [27, 28], 9 for BRVO [29, 30] and 9–10 for CRVO [31–33], with correspondingly inferior outcomes. Boosting injection rates for nAMD, DMO and RVO, or likely longer lasting agents, would be expected to improve outcomes in our patients. Furthermore, the baseline vision does not seem to have improved over time. Starting treatment earlier before significant vision is lost and increasing the availability of rapid access clinics so that our patients are seen and treated promptly could likely improve outcomes in routine clinical practice. Further research is warranted to evaluate whether long-term outcomes have also stabilised, noting that individualised treatment regimens tend to diverge after 12 months and long-term patient compliance remains a significant challenge in routine clinical practice.

SUMMARY

What was known before

- VEGF inhibitors are the standard of care for the treatment of nAMD, DMO and RVO.
- Studies reported that the outcomes in eyes receiving VEGF inhibitors for age-related macular degeneration, DMO and RVO in routine clinical practice were inferior to their pivotal clinical trials.

What this study adds

- Treatment outcomes of nAMD, DMO and RVO in routine clinical practice with VEGF inhibitors have stabilised in the last 5 years.
- The outcomes were reasonably good, but treatment frequency has stabilised at a rate that is lower than those of the clinical trials with correspondingly inferior outcomes.

DATA AVAILABILITY

Data analysed in this analysis cannot be made openly available due to ethical concerns. We encourage to contact the Save Sight Registries at the University of Sydney, Australia (ssi.ssr@sydney.edu.au) for further information about the data and conditions for access.

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AUTHOR CONTRIBUTIONS

Conception and design—SB, VN, DB, MG. Analysis and Interpretation—SB, VN, DB, MG. Data collection—SB, AH, PHG, FV, HM, LM, DS, JA, ILM, DB, MG. Overall responsibility—SB, VN, AH, PHG, FV, HM, LM, DS, JA, ILM, DB, MG.

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Initial response and 12-month outcomes after commencing dexamethasone or vascular endothelial growth factor inhibitors for retinal vein occlusion in the FRB registry

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To compare baseline characteristics, initial response and 12-month efficacy and safety outcomes in eyes with branch and central retinal vein occlusion (BRVO and CRVO) treated with dexamethasone implants (DEX) or anti-vascular endothelial growth factor (anti-VEGF) we performed a multi-centre, retrospective and observational study using Fight Retinal Blindness! Registry. Of 725 eligible eyes, 10% received DEX initially with very frequent adjunctive anti-VEGF (BRVO-DEX 49%, CRVO-DEX 60%). The primary outcome of mean adjusted change in VA at 12 months with DEX and anti-VEGF initiated groups were not statistically significantly different (BRVO: DEX + 6.7, anti-VEGF + 10.6 letters; CRVO: DEX + 2.8, anti-VEGF + 6.8 letters). DEX initiated eyes had fewer injections and visits than anti-VEGF initiated eyes. The BRVO-DEX eyes had greater initial mean changes in VA and central subfield thickness (CST) and achieved inactivity sooner than BRVO-anti-VEGF eyes. The mean CST after the first three months was above 350 µm in all but the BRVO-anti-VEGF group, suggesting undertreatment. In routine care DEX is uncommonly used when available as initial treatment of BRVO and CRVO requiring supplemental anti-VEGF within the first year. The 12-month outcomes were similar, but DEX initiated eyes had fewer injections and visits but more episodes of raised IOP Vs those starting anti-VEGF.

Retinal vein occlusion (RVO), the second most common retinal vascular disease[1], may present in the form of central, hemicentral, or branch retinal vein occlusion[1–5]. The prevalence of RVO it is not influenced by gender and increases with advanced age, being estimated as 0.77% in people aged 30–89 years in 2015 data[6]. This disease is a vision-threatening disorder due not only to the presence of macular oedema (MO) but also to the development of retinal or anterior segment neovascularization.

Retinal vein occlusion generates a cascade of reactions: the capillary pressure increases, ischaemia induces the expression of vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines,

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causing the blood-retinal barrier breakdown and the increase of vascular permeability leading MO and retinal neovascularization[7]. In the long-term, persistence and recurrence of MO leads to irreversible damage to the retina, causing low vision and/or blindness.

Therefore, anti-VEGF and anti-inflammatory drugs are the primary treatment regimens for RVO-MO. Pivotal studies[8–13], clinical practice studies[1–25], meta-analysis and systematic reviews[1,26–30] have demonstrated the efficacy and safety of bevacizumab, ranibizumab, aflibercept and dexamethasone intravitreal implant (DEX; Ozurdex 0.7 mg, Allergan, an AbbVie company, North Chicago, Illinois, USA) for the MO due to RVO. However, comparative studies and meta-analyses have reported conflicting anatomical and functional outcomes[1,31–34].

The aim of this study was to describe baseline patient characteristics and 12-month outcomes in treatment-naïve MO due to RVO initially treated with intravitreal dexamethasone implant or anti-VEGF in routine European clinical practice using the Fight Retinal Blindness (FRB)! Registry.

Methods

Design and setting

This retrospective observational study used anonymized data obtained from the previously described FRB! registry Retinal Vein Occlusion module[17,18]. The registry collects a prospectively defined, minimum outcome set collected via a web-based interface that does not interfere with the treatment and follow-up decisions made by treating physicians in routine care. Therefore, treatment and retreatment decisions and timing were at the discretion of the physician and patient, reflecting the clinical practice. The FRB registry has mandatory fields so, in marked contrast to other databases such as the Intelligent Research in Sight Registry (ClinicalTrials.gov Identifier: NCT02485847), anonymised data accepted by the database in the server at the University of Sydney are 100% complete and within pre-specified ranges. The study adhered to the tenets of the Declaration of Helsinki and followed the STrenghtening the Reporting of Observational studies in Epidemiology (STROBE) checklists for observational studies[35]. Ethics approval was granted in: Spain—Hospital Clínic de Barcelona (HCB/2018/0123); Italy—IRCCS Cà Granda Foundation Maggiore Policlinico Hospital; France—Société Française d'Ophtalmologie (2017_CLER-IRB_ll-05) and data protection approval in the United Kingdom—Caldicott Guardian (Until Sept 2024). Written informed consent was obtained for all patients.

Patient selection and definitions

We included treatment-naïve patients with MO due to CRVO or BRVO that commenced treatment at FRB! centres where the dexamethasone implant (0.7 mg DEX implant; Ozurdex; Allergan, Inc, Irvine, CA) or VEGF inhibitors including ranibizumab (0.5 mg Lucentis, Genentech Inc/Novartis), bevacizumab (1.25 mg Avastin; Genentech, Inc., CA, USA/Roche, Basel, Switzerland) or aflibercept (2 mg Eylea, Bayer) were available as first-line therapy in Spain, France, Italy or the UK between March 1st, 2012, and March 1st, 2022. The study period extended from the first injection (baseline visit) until the 12-month visit (365± 30 days). Participants had at least 3 visits in the first year. Eyes with hemicentral vein occlusion were excluded. "Completers" were defined by follow-up ≥ 335 days. "Adjunctive therapy" was defined by anti-VEGF injections in DEX eyes and steroid injections in eyes initially treated with VEGF inhibitors.

Outcomes

The primary outcome of this study was mean adjusted change in VA at first three months and at 12 months. Secondary outcomes included mean adjusted change in CST, crude changes in mean VA and CST over 12 months; visits and injections (DEX and VEGF inhibitors injections, in total and separately); non-completion; and adverse events.

Statistical analysis

Subgroup analysis was performed by RVO type and initial treatment and included: "BRVO-DEX", "BRVO-VEGF", "CRVO-DEX," and "CRVO-VEGF". Descriptive statistics used counts, percentages, means, standard deviations (SD), medians, and first and third quartiles (Q1, Q3). Comparison of baseline demographics was conducted using Student t-test, Wilcoxon's rank sum, and Fisher's exact test where appropriate. We used generalised additive mixed effects models (GAMMs) to predict VA, and CST outcomes based on initial therapy with either DEX or VEGF mainly to adjust for baseline differences in eyes initially treated with DEX or VEGF. Since we observed high rates of adjunctive VEGF therapy in eyes initially treated with DEX, we took a more descriptive approach (without censorship) to present 12-month outcomes no matter what treatment was delivered. Fixed effects included age and baseline VA (or CST). Nesting of outcomes within the practice or the same patient were considered random effects. Event based outcomes were described with Kaplan–Meier survival analysis, including first grading of inactivity, first use of adjunctive therapy and non-completion. The timing of these events was compared using Cox-proportional hazards models.

Statistical analysis was performed using R version 4.1.3 (http://www.R-project.org/). Models were computed using *mgcv* (1.8–42) package. The *survival* (3.5–3) package was used to generate the Kaplan Meier estimates and *coxme* (2.2–18.1) for comparing event-based outcomes in the subgroup analysis[36].

Results

Patient characteristics and disposition

We identified 725 treatment naïve eyes with BRVO (407 eyes) or CRVO (318 eyes) that started treatment at European FRB! centres where DEX and VEGF inhibitors were available as first-line therapy between March 1, 2012, and 2022. Ten percent (72/725 eyes) received the DEX implant as initial therapy, including 12% (47/407) of

BRVO eyes and 8% (25/318) of CRVO eyes. The remainder were initially treated with VEGF inhibitors, including bevacizumab in 6% (41/725), ranibizumab in 50% (363/725), or aflibercept in 34% (249/725) (Table 1).

CRVO eyes starting DEX had better mean baseline VA than CRVO-VEGF eyes (49 versus 36 letters, respectively; $P=0.01$). BRVO eyes starting DEX were similar in most respects to eyes starting VEGF inhibitors (Table 1), but fewer BRVO-DEX eyes had good VA ≥ 70 letters than BRVO-VEGF eyes (17% versus 33%, respectively; $P=0.04$).

Visual outcomes

Initial treatment response that can be attributed to DEX or VEGF inhibitors was larger in BRVO with DEX than with VEGF inhibitors at 1 and 2 months (BRVO: mean changes in VA at months 1, 2 and 3: BRVO-DEX: + 11, + 14, + 10 letters; BRVO-VEGF + 3, + 5, + 11 letters; $P=0.003$, $P<0.001$, $P=0.91$, respectively). In CRVO the initial response was similar after DEX and VEGF inhibitors (Table 2) however CRVO-DEX eyes did start with significantly better baseline VA.

12-month outcomes reflect combination therapy in many eyes, particularly the DEX groups because of widespread adjunctive VEGF inhibitors therapy during the 12-month study. Nevertheless, the primary outcome of mean 12-month adjusted change in VA (95% CI) in BRVO eyes was + 6.7 (+ 1.8, + 11.7) letters when initially treated with DEX and + 11.7 (+ 9.2, + 13.2) letters with VEGF inhibitors; in CRVO it was + 2.8 (− 6.8, + 12.4) letters when initially treated with DEX and + 6.8 (+ 3.3, + 10.3) letters with VEGF inhibitors. The confidence intervals overlap at 12 months in Fig. 1C and D.

Anatomical outcomes

Initial anatomical response was larger in BRVO with DEX than with VEGF inhibitors at 1 and 2 months (DEX-BRVO: mean changes in CST at months 1, 2 and 3: DEX: − 162 µm, − 215 µm, − 135 µm; VEGF-BRVO: − 46 µm, − 61 µm, − 133 µm; $P<0.001$, $P<0.001$, $P=0.99$, respectively). The trend reversed significantly in favour of VEGF inhibitor-initiated eyes between 3 and 10 months (Fig. 1G). Despite BRVO-DEX eyes having the lowest mean CST of any group during the study, 282 µm at 2 months, mean CST was 395 µm at 4 months and stayed at or above 350 µm for the remainder of the year. The macular thickness in BRVO-VEGF was better maintained at around 325 µm from 3 to 12 months (Fig. 1E).

The DEX and VEGF inhibitors initiated CRVO eyes had similar early unadjusted reductions in CST with the exception of greater change in CST with DEX at month 2 (DEX-CRVO: mean changes in CST at months 1, 2, and 3: DEX: − 144 µm, − 231 µm, − 195 µm; VEGF-CRVO: − 65 µm, − 99 µm, − 188 µm; $P=0.15$, $P=0.02$, $P=0.89$, respectively). After 3 months, the mean CST was generally higher in CRVO-DEX eyes than in CRVO-VEGF eyes (Fig. 1). In both CRVO groups, the mean CST generally remained above 350 µm during the remainder of study (Fig. 1C,D).

The 12-month adjusted mean change in CST (95% CI) in BRVO-DEX eyes was − 107 µm (− 151, − 62) and in BRVO-VEGF eyes was − 155 µm (− 172, − 138), in CRVO-DEX it was − 207 µm (− 276, − 139), and in CRVO-VEGF eyes it was − 248 µm (− 280, − 215) with overlapping confidence intervals in both BRVO and CRVO at 12 months (Fig. 1G,H).

	BRVO-DEX	BRVO-VEGF	P value	CRVO-DEX	CRVO-VEGF	P value
Eyes, n (% of RVO type)	47 (12%)	360 (88%)		25 (8%)	293 (92%)	
Gender, % females	51%	51%	0.93	48%	48%	1.0
Age, mean years (SD)	68 (10)	70 (12)	0.40	69 (11)	72 (12)	0.22
Baseline VA, mean letters (SD)*	51 (20)	55 (21)	0.17	49 (22)	36 (27)	**0.01**
VA ≥ 70 letters, %	17%	33%	**0.04**	20%	15%	0.57
VA ≤ 35 letters, %	21%	19%	0.92	32%	47%	0.20
CST, mean microns (SD)	523 (167)	473 (157)	0.07	594 (228)	610 (226)	0.75
Hypertensive, %	49%	62%	**0.04**	72%	57%	0.25
Glaucoma, %	2%	6%	0.50	0%	13%	0.06
Pseudophakia, %	21%	17%	0.59	28%	21%	0.59
Initial agent						
Dexamethasone implant, n (%)	47 (100%)			25 (100%)		
Bevacizumab, n (%)		28 (8%)			13 (4%)	
Ranibizumab, n (%)		204 (57%)			159 (54%)	
Aflibercept, n (%)		128 (36%)			121 (41%)	

Table 1. Baseline characteristics of treatment naïve patients with BRVO or CRVO initially treated with DEX or VEGF inhibitors. Significant values are in bold. *Number of letters read on a logarithm of the minimum angle of resolution VA chart. *BRVO-DEX* BRVO eyes initially treated with DEX, *BRVO-VEGF* BRVO eyes initially treated with VEGF inhibitors, *CRVO-DEX* CRVO eyes initially treated with DEX, *CRVO-VEGF* CRVO eyes initially treated with VEGF inhibitors, *VA* Visual Acuity; *CST* Central Subfield Thickness, *SD* Standard Deviation.

	DEX-BRVO	VEGF-BRVO	P value	DEX-CRVO	VEGF-CRVO	P value
Visual acuity (VA, letters)						
1 m Δ VA, mean (95% CI)	+ 11 (7, 16)	+ 3 (2, 4)	**0.001**	+ 6 (1, 11)	+ 3 (2, 5)	0.26
2 m Δ VA, mean (95% CI)	+ 14 (9, 19)	+ 5 (4, 6)	**0.002**	+ 5 (− 2, 13)	+ 5 (3, 7)	0.96
3 m Δ VA, mean (95% CI)	+ 10 (5, 16)	+ 11 (9, 12)	0.92	+ 2 (− 6, 10)	+ 10 (7, 12)	0.10
6 m Δ VA, mean (95% CI)	+ 9 (4, 13)	+ 11 (10, 13)	0.28	+ 3 (− 7, 13)	+ 8 (5, 11)	0.37
12 m Δ VA, mean (95% CI)	+ 6 (0, 12)	+ 11 (9, 13)	0.18	+ 0 (− 10, 10)	+ 7 (5, 10)	0.16
12 m adjusted Δ VA, mean (95% CI) *	+ 6.7 (+ 1.8, + 11.7)	+ 11.7 (+ 9.2, + 13.2)		+ 2.8 (− 6.8, + 12.4)	+ 6.8 (+ 3.3, + 10.3)	
12 m gained ≥ 15 letters, %	34%	36%	0.93	20%	35%	0.18
12 m lost ≥ 15 letters, %	15%	6%	0.07	20%	15%	0.56
Central subfield thickness (CST, μm)						
1 m Δ CST, mean (95% CI)	− 162 (− 210, − 113)	− 46 (− 59, − 33)	< **0.001**	− 144 (− 247, − 42)	− 65 (− 85, − 44)	0.15
2 m Δ CST, mean (95% CI)	− 215 (− 269, − 160)	− 61 (− 75, − 48)	< **0.001**	− 231 (− 333, − 130)	− 99 (− 123, − 76)	**0.02**
3 m Δ CST, mean (95% CI)	− 135 (− 193, − 77)	− 135 (− 153, − 117)	0.99	− 195 (− 288, − 102)	− 188 (− 218, − 159)	0.89
6 m Δ CST, mean (95% CI)	384 (159)	328 (109)	0.71	390 (155)	387 (216)	0.97
12 m Δ CST, mean (95% CI)	− 110 (− 167, − 53)	− 143 (− 161, − 126)	0.28	− 217 (− 317, − 117)	− 192 (− 221, − 164)	0.65
12 m adjusted Δ CST, mean (95% CI) *	− 107 (− 151, − 62)	− 155 (− 172, − 138)		− 207 (− 276, − 139)	− 248 (− 280, − 215)	
12 m completers, n (%)	40/47 (85%)	288/360 (80%)		22/25 (88%)	226/293 (77%)	0.19
Injections and visits						
Total injections, median (Q1, Q3)**	4 (3, 5)	7 (5, 8)	< **0.001**	3 (3, 6)	7 (5, 9)	< **0.001**
DEX injections, mean	2.1	0.1		1.8	0.2	
VEGF injections, mean	1.8	5.9		2.2	6.2	
Visits, median (Q1, Q3)**	9 (7, 11)	10 (8, 12)	0.15	9 (7, 11)	12 (9, 14)	**0.002**
Adjunctive therapy used, n (%)#	23 (49%)	37 (10%)	< **0.001**	15 (60%)	31 (11%)	**0.002**
VEGF injections, median (Q1, Q3)**	1 (0, 3)	6 (4, 8)		2 (0, 4)	7 (4, 9)	
DEX injections, median (Q1, Q3)**	2 (1, 3)	0 (0, 0)		2 (1, 2)	0 (0, 0)	
Additional treatment & adverse outcomes						
Sectoral or PRP laser, n (%)	5 (11%)	52 (14%)	0.65	3 (12%)	129 (44%)	0.03
Focal/macular laser, n (%)	1 (2%)	6 (2%)	0.58	0 (0%)	3 (1%)	1.0
Elevated IOP req. treatment, n (%)	5 (11%)	9 (2%)	**0.015**	4 (16%)	17 (6%)	0.07
Cataract surgery, n (%)	2 (4%)	23 (6%)	0.75	1 (4%)	16 (5%)	1.0
Neovascular complications, n (%)***	1 (2%)	7 (2%)	1.0	2 (8%)	31 (11%)	0.94
Neovascular glaucoma specifically, n (%)	0 (0%)	1 (0%)	1.00	1 (4%)	22 (8%)	0.80
Macular changes affecting vision, n (%)****	7 (15%)	47 (13%)	0.90	4 (16%)	39 (13%)	0.94

Table 2. Outcomes based on initial treatment and RVO type. Significant values are in bold. *Generalised mixed effects models were used for adjustment and 95% confidence intervals: Fixed effects—baseline VA (CST) and age. Random effects—nesting in practices and bilateral disease. The confidence intervals all overlapped at 12 months despite significant differences at other times in the models in both BRVO (VA: $P < 0.001$, CST: $P < 0.001$) and CRVO (VA: $P = 0.047$, CST: $P < 0.001$) eyes initially treated with DEX or VEGF. **Total injections of any drug calculated on Completers only ***Neovascular Complications in either the anterior or posterior segment ****Macular hole/Epiretinal membrane/Pigmentary macular changes judged by the treating physician as affecting visual acuity. *BRVO-DEX* BRVO eyes initially treated with DEX, *BRVO-VEGF* BRVO eyes initially treated with VEGF inhibitors, *CRVO-DEX* CRVO eyes initially treated with DEX, *CRVO-VEGF* CRVO eyes initially treated with VEGF inhibitors, *Δ* Change; *1 m, 2 m, 3 m, 12 m* 1-, 2-, 3-, 12-month, *n* number, *VA* Visual Acuity in letters read on a logarithm of the minimum angle of resolution VA chart (best of uncorrected, corrected or pinhole), *SD* Standard Deviation, *CI* Confidence interval, *Q1, Q3* Interquartile range, *PRP* Panretinal photocoagulation (number of patients that received it rather than the number of treatments), *IOP* Intraocular pressure where req. treatment included selective laser trabeculoplasty or topical antihypertensive agents.

Injections, visits

The BRVO-DEX 12-month completers (40/47 [85%]) had a median (Q1, Q3) of 4 injections (3, 5) in total, fewer than the BRVO-VEGF eyes with 7 injections (5, 8) ($P < 0.001$) but we found no significant difference in the frequency of visits in BRVO groups (median, DEX, 9 visits; VEGF, 10 visits; $P = 0.15$). The CRVO-DEX 12-month completers (22/25 [88%]) had a median (Q1, Q3) of 3 injections (3, 6) in total and 9 visits (7, 11), fewer than the 7 injections (5, 9) and fewer than the 12 visits (9, 14) in CRVO-VEGF eyes ($P < 0.001$, $P = 0.002$). The median (Q1, Q3) time between first and second DEX injections was 175 days (129, 243).

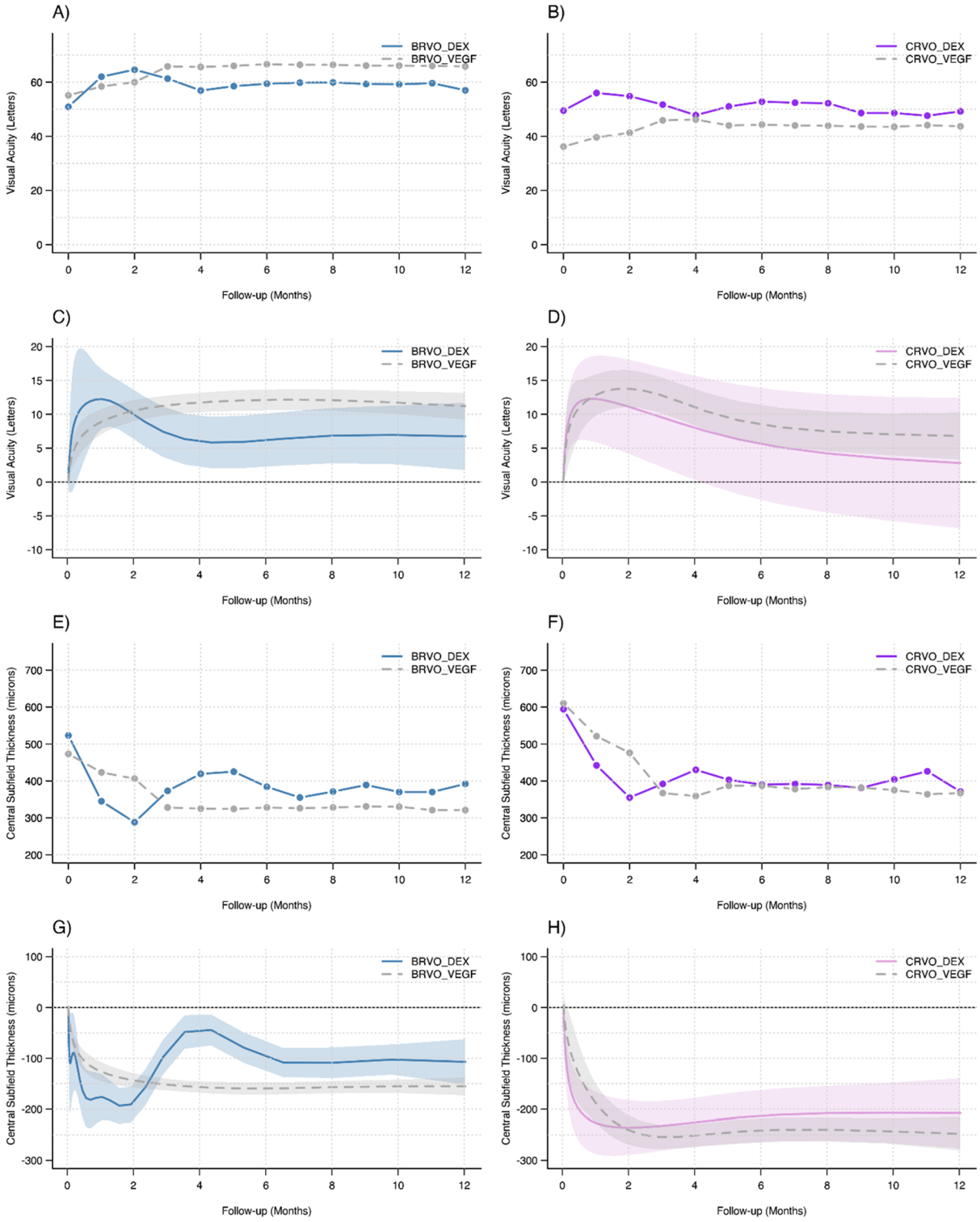

Figure 1. Unadjusted and Adjusted outcomes by RVO type after initial treatment with DEX or VEGF inhibitors. Unadjusted plots include mean VA (**A**, **B**) and mean CST (**E**, **F**). Generalised additive mixed effects models were generated to plot Adjusted Change in VA (**C**, **D**) and Adjusted Change in CST (**G**, **H**) with 95% confidence intervals shaded. The confidence intervals all overlapped at 12 months despite significant differences at other times.

Inactivity, adjunctive therapy, and non-completion

Time to first grading of inactivity, adjunctive therapy and loss to follow-up were analysed with Kaplan–Meier estimates by initial treatment with DEX or VEGF inhibitors (Fig. 2). BRVO-DEX eyes were more likely to achieve

inactivity than BRVO-VEGF eyes after adjustment with Cox-proportional hazards models ($P = 0.01$), no significant difference was found in CRVO ($P = 0.9$). The proportion of DEX initiated eyes receiving adjunctive VEGF inhibitors therapy with BRVO was 49% and with CRVO 60% compared with adjunctive DEX therapy in BRVO-VEGF and CRVO-VEGF eyes (both 10%; both $P < 0.001$, Fig. 2). Table 3 describes outcomes in DEX initiated eyes that appeared to benefit from additional VEGF inhibitors rescue therapy compared with those remaining on DEX monotherapy. Non-completion rates were similar (Fig. 2, BRVO-DEX 7/47 [15%], BRVO-VEGF eyes 72/360 [20%]; $P = 0.17$, and CRVO-DEX 3/25 [12%], CRVO-VEGF 67/293 [23%]; $P = 0.19$).

Adverse outcomes

We found a higher rate of elevated IOP requiring treatment in BRVO (DEX 5/47 [11%] vs. VEGF inhibitors treated eyes 9/360 [2%]; $P = 0.015$). Elevations in IOP of > 10 mmHg from baseline IOP occurred more frequently in DEX eyes (42/80 [52%], at a median [Q1, Q3] 109 days [70, 199]) compared with VEGF eyes (79/721 eyes [11%]; $P < 0.01$, at a median [Q1, Q3] of 168 days [112, 253]). The earliest occurrence of an elevation in IOP of > 10 mmHg occurred 25 days after a DEX injection. No other significant difference in cataract surgery, new macular changes affecting vision (epiretinal membrane, macular hole, pigment clumping, or atrophy) or neovascular complications based on initial DEX or VEGF inhibitors treatment in BRVO or CRVO. The higher rate of PRP in CRVO-VEGF eyes reflected individual practice patterns from one large practice centre that mainly used VEGF inhibitors as initial therapy. Overall, a total of 4311 injections (including 239 DEX-implants) were delivered in the study with one retinal detachment (BRVO-VEGF), one iatrogenic cataract (BRVO-VEGF), and one case of infectious endophthalmitis (CRVO-VEGF).

Discussion

This observational study using data from the prospectively designed RVO module of the FRB! registry recruited eyes at European centres where both VEGF inhibitors and DEX were available for treatment naïve MO due to RVO found that DEX was used in only around 10% of eyes but outcomes at 12 months were similar to the majority that were initially treated with VEGF inhibitors. Our analysis adjusted for baseline differences including significantly higher VA in CRVO eyes initially treated with DEX rather than VEGF inhibitors. We found no significant difference in the primary outcome at 12 months of mean adjusted change in VA based on initial treatment with DEX or VEGF inhibitors of BRVO (DEX + 6.7 letters, BRVO + 11.7 letters) or CRVO (DEX + 2.8 letters, VEGF + 6.8 letters). Significant secondary outcomes included higher rates of adjunctive therapy use after initial DEX (BRVO 49% and CRVO 60% VEGF inhibitors use) than initial VEGF inhibitors (10% DEX use), inactivity earlier in BRVO after DEX than VEGF inhibitors; fewer injections in both BRVO and CRVO after DEX than VEGF inhibitors; fewer visits in CRVO after DEX than VEGF inhibitors; and higher rate of elevated IOP requiring treatment in BRVO after DEX than VEGF inhibitors.

We found no significant difference based on initial treatment with DEX or VEGF inhibitors in 12-month mean adjusted change in CST in BRVO or CRVO, time to inactivity in CRVO, frequency of visits in BRVO. About three quarters of eyes were phakic at baseline and there was no significant difference in rates of cataract surgery in the first year of treatment, although other comparative studies of retinal vascular disease have identified higher rates of cataract surgery with DEX from the second year[22].

The 12-month outcomes in this study were not a comparison of VEGF inhibitors and DEX monotherapy as there was widespread adjunctive VEGF inhibitors after initial treatment with DEX. This led us to analyse initial response that could be attributed uniquely to DEX or VEGF inhibitors. In CRVO, even though DEX initiated eyes had higher baseline VA, the mean change in VA at 2 months was larger than CRVO-VEGF eyes. In BRVO we observed impressive initial response to DEX with significantly larger improvements in mean VA and CST at months 1 and 2, and inactivity was achieved earlier with DEX than with initial VEGF inhibitors.

The efficacy of initial DEX waned beyond 3 months in both BRVO-DEX and CRVO-DEX groups, likely compromising 12-month outcomes. BRVO-DEX eyes were most affected with mean CST almost returning to baseline by 4 months with limited recovery subsequently. The CRVO-DEX group had a similar set back in mean CST at 4 months, but a higher proportion received rescue VEGF inhibitors injections. The VEGF inhibitors initiated groups achieved improvements more gradually and better maintained them through 12 months.

This study adds real-world evidence to pivotal trial evidence suggesting DEX therapy usually needs be delivered more frequently than 6-monthly in RVO to maintain outcomes. The saw-tooth pattern in mean CST in the GENEVA study suggested efficacy of DEX waned before 6 months. The proportion of patients with VA ≥ 15 letters from baseline was maximal at day 30 (15.0%) and day 60 (17.6%) but the study failed to demonstrate a difference between DEX and sham at 180 days (6.5% [95% CI − 0.9% to 13.9%])[8]. Nevertheless, this led to approval of DEX as initial therapy in RVO in Italy, France, Spain, and the UK with an initial 6-month limit on re-treatment. It remains unclear if more frequent retreatment using DEX monotherapy could make it a more viable initial treatment option in RVO. We believe the widespread uptake of adjunctive VEGF inhibitors therapy after initial DEX treatment reflects an attempt to counter undertreatment associated with what was typically a 6-month treatment interval between injections of DEX in this study.

Generalised undertreatment in this study also likely affected outcomes in all but the BRVO-VEGF group. The BRVO-DEX, CRVO-DEX and CRVO-VEGF groups consistently had mean CST above 350 µm in the latter part of the study. Only the BRVO-VEGF group maintained mean CST around 325 µm from 3 to 12 months. Less impressive outcomes in routine care are often blamed on treatment burden. Even though fewer injections and visits were observed after starting DEX, it was subsequent undertreatment that likely explains the less impressive 12-month VA and CST outcomes in this study compared with pivotal studies[8–11,13] and other real-world studies[19,20,31–34]. The baseline VA was generally better in this study than previous reports from our group[17,18]. In

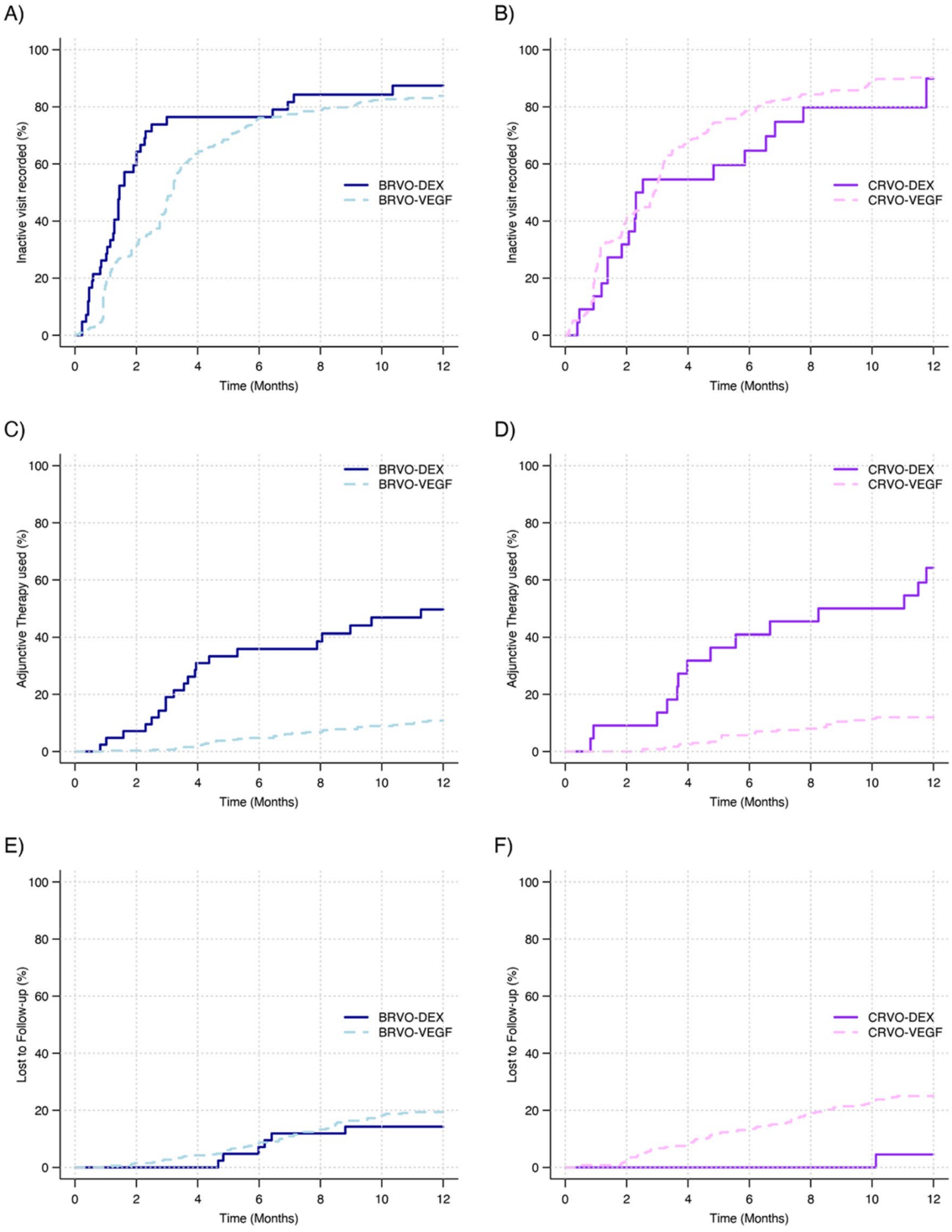

Figure 2. Kaplan Meier survival curves for time to first grading of inactivity, use of adjunctive therapy (VEGF in DEX eyes/DEX in VEGF eyes), and loss to follow-up by RVO type and initial treatment with DEX or VEGF inhibitors.

particular, the high baseline VA in the CRVO-DEX eyes would have left less room for improvement, though we did adjust for that.

Ocular hypertension is a known side effect of intravitreal dexamethasone implant occurring at 6 to 8 weeks and returning to baseline by around 3 to 4 months and could be managed by topical anti-glaucoma medications in 90% eyes (14,26). Similar too previous studies (14, 26) we found a higher rate of elevated IOP requiring treatment in the DEX initiated eyes compared with VEGF initiated eyes (BRVO-DEX 5/47 [11%] vs. BRVO-VEGF 9/360 [2%]; $P = 0.015$; and CRVO-DEX 4/25 [16%] vs CRVO-VEGF 17/293 [6%]; $P = 0.07$). The data

	BRVO-DEX DEX monotherapy	BRVO-DEX adjunctive VEGF therapy	CRVO-DEX DEX monotherapy	CRVO-DEX adjunctive VEGF therapy
12 m completers/eyes, n (%)	20/24 (83%)	20/23 (87%)	9/10 (90%)	13/15 (87%)
Visual acuity (VA, letters)				
1 m Δ VA, mean (95% CI)	+9 (4, 14)	+13 (5, 21)	+5 (− 3, 13)	+7 (1, 14)
2 m Δ VA, mean (95% CI)	+13 (8, 18)	+15 (5, 24)	+2 (− 9, 12)	+8 (− 3, 18)
3 m Δ VA, mean (95% CI)	+8 (3, 14)	+12 (4, 21)	+1 (− 11, 13)	+3 (− 8, 14)
6 m Δ VA, mean (95% CI)	+4 (− 2, 11)	+13 (6, 20)	+7 (− 9, 22)	− 2 (− 11, 7)
12 m Δ VA, mean (95% CI)	+2 (− 5, 9)	+10 (0, 21)	− 5 (− 18, 8)	+3 (− 11, 17)
12 m gained ≥ 15 letters, %	21%	48%	10%	27%
12 m lost ≥ 15 letters, %	17%	13%	30%	13%
Central subfield thickness (CST, μm)				
1 m Δ CST, mean (95% CI)	− 168 (− 241, − 95)	− 155 (− 220, − 90)	− 157 (− 280, − 34)	− 136 (− 289, 17)
2 m Δ CST, mean (95% CI)	− 210 (− 282, − 138)	− 220 (− 303, − 137)	− 231 (− 339, − 123)	− 231 (− 388, − 75)
3 m Δ CST, mean (95% CI)	− 135 (− 217, − 53)	− 135 (− 217, − 53)	− 224 (− 327, − 121)	− 176 (− 317, − 34)
6 m Δ CST, mean (95% CI)	− 124 (− 195, − 53)	− 142 (− 239, − 44)	− 265 (− 433, − 96)	− 159 (− 241, − 77)
12 m Δ CST, mean (95% CI)	− 121 (− 196, − 46)	− 98 (− 185, − 12)	− 113 (− 189, − 36)	− 286 (− 437, − 135)
Injections and visits				
Total injections, median (Q1, Q3)**	2 (2, 3)	6 (4, 6)	2 (2, 3)	5 (4, 6)
DEX injections, mean	2.3	1.8	2.3	1.5
VEGF injections, mean	0	3.7	0	3.7
Visits, median (Q1, Q3)**	8 (7, 11)	10 (8, 11)	8 (7, 9)	9 (7, 12)
Adjunctive therapy used, n (%)#	0 (0%)	23 (100%)	0 (0%)	15 (100%)
VEGF injections, median (Q1, Q3) **	0 (0, 0)	3 (2, 5)	0 (0, 0)	4 (2, 5)
DEX injections, median (Q1, Q3) **	2 (2, 3)	2 (1, 3)	2 (2, 3)	1 (1, 2)
Additional treatment & adverse outcomes				
Sectoral or PRP laser, n (%)	3 (12%)	2 (9%)	1 (10%)	2 (13%)
Focal/macular laser, n (%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Elevated IOP req. treatment, n (%)	2 (8%)	3 (13%)	0 (0%)	4 (27%)
Cataract surgery, n (%)	2 (8%)	0 (0%)	1 (10%)	0 (0%)
Neovascular complications, n (%)***	0 (0%)	1 (4%)	0 (0%)	2 (13%)
Neovascular glaucoma specifically, n (%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Macular changes affecting vision, n (%)****	3 (12%)	4 (17%)	3 (30%)	1 (7%)

Table 3. Outcomes in BRVO-DEX and CRVO-DEX eyes based on treatment received being DEX monotherapy or a combination of DEX and Adjunctive VEGF therapy. **Total injections of any drug calculated on Completers only ***Neovascular Complications in either the anterior or posterior segment ****Macular hole/Epiretinal membrane/Pigmentary macular changes judged by the treating physician as affecting visual acuity. *Δ* Change, *1 m, 2 m, 3 m, 12 m* 1-, 2-, 3-, 12-month, *n* number, *VA* Visual Acuity in letters read on a logarithm of the minimum angle of resolution VA chart (best of uncorrected, corrected or pinhole), *SD* Standard Deviation, *CI* Confidence interval, *Q1, Q3* Interquartile range, *PRP* Panretinal photocoagulation (number of patients that received it rather than the number of treatments), *IOP* Intraocular pressure where req. treatment included selective laser trabeculoplasty or topical antihypertensive agents.

field "IOP elevations requiring treatment" collected in the registry encompasses a wider variety of definitions (i.e. IOP ≥ 25/30/35, IOP change ≥ 5/10/15, etc.) and in our opinion is more clinically relevant, as it takes into account individual considerations in each specific case (i.e. glaucoma eyes, cupped discs, etc.), although we do acknowledge that this may contribute to explain slight differences to benchmark our data with other series. Mun et al.[23] considered that the side effects of steroids caused physicians consider anti-VEGF agents as a first-line drug and we think that could be a cause of delay in treatment or even undertreatment as physician dedicate follow-up visits to treating adverse effects and leave aside the treatment of macular edema until the adverse effect resolved.

In the absence of any other difference, such as macular changes affecting vision, we do believe that the numerically higher rate of losing ≥ 15 letters in the DEX groups was likely due to development of cataract secondary to the use of intraocular steroid. It is not surprising though that the rates of cataract surgery were similar in DEX and VEGF groups because the study spanned only first 12 months after therapy commenced leaving little time to schedule and complete cataract surgery. Longer term follow-up with more patients would be required to confirm this point as Garay-Aramburu et al.[22] reported in a five-year follow-up study. Furthermore, we observed no statistically significant differences between both groups regarding additional treatments and adverse outcomes, which included focal and PRP laser, cataract surgeries, neovascular complications, neovascular glaucoma and macular changes affecting vision. We do believe that the limited 12 months timespan of the study could also explain these results.

This study has inherent weaknesses associated with the use of observational data from a real-world database[16–20,27]. In contrast to randomized controlled trials (RCT), treatment and retreatment decisions including timing are based on the physician´s observation and in accordance with the patient, resulting in a heterogeneity of treatment. This heterogeneity is influenced by the introduction of drugs, their efficacies and cost, the resources at the different sites, burden related to treatment[23,29], the span of the study and the differences between Clinical Guidelines[2,4]; but, despite this heterogeneity, the outcomes reported by real-world studies contribute to these Guidelines[23].

As with other real-world studies[16–20,27], several RCTs[1,31,32] and meta-analyses[28–30], our dataset did not differentiate between ischemic and non-ischemic RVO when reporting outcomes. Ang et al.[27] reviewed 48 real-world studies of BRVO. Because of generally poor reporting of ischaemia in the 71 treatment arms included in that meta-analysis, whether macular or peripheral, they found divergent results regarding the effect of ischaemia on visual acuity gains at least in BRVO when treated with intravitreal therapy. Our study reported that 44% of the CRVO-VEGF patients received PRP—a relatively high proportion—manly because one centre seemingly performing it routinely. There is no consensus on routine delivery of PRP in CRVO within the clinical guidelines[2,4]. Li et al.[37] published a systematic review indicating that laser photocoagulation did not appear to be effective in modifying the visual acuity outcomes. The implication being that PRP should probably be reserved for neovascular complications. Nevertheless, that study suggests that the visual outcomes were likely not influenced by having one centre perform PRP at a higher rate than usual. The weaknesses of the retrospective nature of our study were compensated for to some extent by the strength of the FRB registry that forces the completion of all fields within pre-specified ranges ensuring data integrity. Besides, follow-up was excellent compared with similar studies[33], but we were unable to fairly compare DEX and VEGF inhibitors over 12-months because of the confounding effect of adjunctive VEGF inhibitors therapy.

The strength of this study is the comparison of initial response to DEX compared with VEGF. The study also identifies how adjunctive VEGF inhibition is required in order to salvage outcomes when a limit of 6 months is placed on DEX retreatment. More frequent retreatment would be required for DEX monotherapy to become a viable alternative to VEGF inhibitors in RVO while still possibly reduce burden of therapy, although the impact on rates of raised intraocular pressure would need to be considered.

In conclusion, this study identified infrequent use of DEX as initial therapy in routine care for RVO despite superior initial response particularly in BRVO compared with VEGF inhibitors. Outcomes were similar at 12 months in both BRVO and CRVO after DEX or VEGF inhibitors as initial treatment. Following initial treatment with DEX, subsequent outcomes suffered due to the 6-month limit on DEX retreatment necessitating frequent VEGF inhibitors rescue therapy. The real-world practice patterns detailed in this manuscript suggest that more robust treatment strategies are required to optimize the clinical outcomes in RVO patients.

Data availability

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

GGA, CA and JZ-V wrote the paper. AH with MG drafted and revised the statistical analysis plan, cleaned, and analysed the data, drafted and revised the paper. MG is inventor of the software used to collect the data for this analysis, initiated the collaborative project, designed and revised the paper. HM, AI, PHG, TG and BW revised the paper.

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Competing interests

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Intraocular Pressure Changes and Vascular Endothelial Growth Factor Inhibitor Use in Various Retinal Diseases: Long-Term Outcomes in Routine Clinical Practice

Data from the Fight Retinal Blindness! Registry

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Purpose: To report long-term changes in intraocular pressure (IOP) in eyes receiving vascular endothelial growth factor (VEGF) inhibitors for various retinal conditions over 12 and 24 months in routine clinical practice.

Design: Retrospective analysis of data from a prospectively designed observational outcomes registry, the Fight Retinal Blindness! Project.

Participants: Treatment-naïve eyes receiving monotherapy with VEGF inhibitors (ranibizumab [0.5 mg], aflibercept [2 mg], or bevacizumab [1 mg]) with at least 3 injections from December 2013 through December 31, 2018, and at least 12 months of follow-up.

Methods: Intraocular pressure was measured at each clinical visit for all eyes as part of routine practice.

Main Outcome Measures: The primary outcome was the mean change in IOP (in millimeters of mercury) at 12 months. The following secondary IOP outcome measures were investigated at 12 and 24 months: (1) mean change in IOP from baseline and (2) proportion of clinically significant IOP increase defined as an elevation of at least 6 mmHg to an IOP of more than 21 mmHg at any point during the follow-up.

Results: We identified 3429 treatment-naïve eyes (395 receiving bevacizumab, 1138 receiving aflibercept, and 1896 receiving ranibizumab) with complete IOP data from 3032 patients with 12 months of follow-up data, of which 2125 (62%) had 24 months of follow-up data. The overall mean IOP change was −0.5 mmHg (95% confidence interval CI, −0.6 to −0.3 mmHg) at 12 months and −0.4 mmHg (95% CI, −0.6 to −0.3 mmHg) at 24 months, whereas the proportions of clinically significant IOP increases were 5.6% and 8.8%, respectively. A lower mean IOP change and fewer IOP elevations at 12 and 24 months was observed in eyes receiving aflibercept than in those receiving bevacizumab and ranibizumab ($P \leq 0.01$ for both comparisons at each time point and outcome). Eyes with pre-existing glaucoma demonstrated more IOP increases over 12 and 24 months (odds ratio [OR], 2.2 [95% CI, 1.2−3.8; $P = 0.012$] and 2.1 [95% CI, 1.1−3.8; $P = 0.025$], respectively).

Conclusions: Mean IOP did not change significantly from baseline to 12 and 24 months in eyes receiving VEGF inhibitors, whereas clinically significant IOP elevations occurred in a small proportion of eyes. Aflibercept was associated with fewer clinically significant IOP elevations, whereas eyes with pre-existing glaucoma were at a higher risk. *Ophthalmology Retina 2020;4:861-870 © 2020 by the American Academy of Ophthalmology*

Supplemental material is available at www.ophthalmologyretina.org.

See Editorial on page 859.

Despite the widespread use of vascular endothelial growth factor (VEGF) inhibitors for retinal conditions, such as neovascular age-related macular degeneration (AMD), diabetic macular edema (DME) and macular edema (ME) secondary to retinal vein occlusion (RVO), the data on their effect on IOP remain limited. It is well known that a transient spike in intraocular pressure (IOP) occurs immediately after an injection, but this quickly decreases over the next 15 minutes for most patients.[1−3] The degree to which anti-VEGF agent injections contribute to long-term IOP changes is less clear. A large real-world study using the Intelligent Research in Sight Registry reported a slight but significant decrease in IOP from baseline in eyes treated with anti-VEGF agents for more than 1 year compared with

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control eyes.[4] Moreover, 2.6% of the treated patients experienced clinically significant, sustained IOP elevations, confirming the results of previous studies.[5–8] Somewhat surprisingly, fewer cases of sustained IOP elevations occurred in eyes treated with aflibercept (1.9%) than with those receiving ranibizumab (2.8%) or bevacizumab (2.8%).[4,5] A recent review highlighted the conflicting reports with regard to IOP changes and the risk factors for IOP rises with intravitreal injections of VEGF inhibitors, which in part may be the result of variability in methodology and the definition of clinically significant IOP increase between studies.[9] More data are needed on long-term IOP change outcomes and the potential risk factors associated with IOP change in patients treated with VEGF inhibitors. This study aimed to explore changes in IOP in eyes receiving VEGF inhibitors for various retinal conditions over 12 and 24 months in routine clinical practice.

Methods

Design and Setting

This was a retrospective analysis of treatment-naïve eyes that had received intravitreal anti-VEGF agents for various retinal diseases in routine clinical practice tracked in the prospectively designed observational database The Fight Retinal Blindness! Registry.[10] Participants in this analysis included patients from practices in Australia, France, New Zealand, Singapore, and Switzerland. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the Southern Eastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (Société Française d'Ophtalmologie IRB), SingHealth Singapore, and the Cantonal Ethics Committee Zurich. All patients gave their informed consent. Informed consent (opt-in consent) was sought from patients in France, Singapore, and Switzerland. Ethics committees in Australia and New Zealand approved the use of opt-out patient consent. This study adhered to the tenets of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology statements for reporting observational studies.[11]

Data Sources and Measurements

The Fight Retinal Blindness! Registry has several modules that collect data from eyes being treated for neovascular AMD, DME, and ME secondary to RVO.[10] Data were obtained prospectively from each clinical visit including IOP measurement (in millimeters of mercury), treatment given, if any, and ocular adverse events. Demographic characteristics (age and gender), initial diagnosis (AMD, DME, or RVO), history of any ocular condition (pre-existing glaucoma status), and whether the eye received prior treatment (cataract surgery and vitrectomy) were recorded at baseline visit. Treatment decisions, including the choice of drug and injection frequency, were at the discretion of the physician in consultation with the patient, thereby reflecting real-world practice. Data on glaucoma treatment during follow-up such as introduction of IOP-lowering drops, laser therapy, or incisional glaucoma surgery were not recorded systematically in any of the 3 modules.

Patient Selection and Groups

Treatment-naïve eyes that received intravitreal monotherapy of VEGF inhibitors (eyes were excluded if switched or if they received any other type of intravitreal treatment) with either aflibercept (2 mg; Eylea [Regeneron, Inc, Tarrytown, NY, or Bayer), bevacizumab (1.25 mg; Avastin [Genentech, Inc/Roche]), or ranibizumab (0.5 mg; Lucentis [Genentech, Inc./Novartis]) for neovascular AMD, DME, or ME secondary to RVO with a minimum of 3 injections and at least 1 year of follow-up, including IOP measurement at least at baseline and 12 months after starting treatment from December 1, 2013, through December 31, 2018, were studied.

Prefilled syringes for administering ranibizumab were approved in early 2015, and global uptake of these prefilled syringes among clinicians using ranibizumab increased gradually over time. Prefilled packing generally was adopted in early 2017. To analyze the effect of prefilled versus nonprefilled syringes on IOP, we analyzed the subset of eyes initially treated with intravitreal ranibizumab injection from January 1, 2017 (prefilled group), with those initially treated with intravitreal ranibizumab injection before January 1, 2014, and January 1, 2013 (nonprefilled group), thereby allowing 12 and 24 months of follow-up, respectively, before the start of prefilled packaging. Patients also were grouped by the total number of injections received: low (3–4 or 3–9 injections), medium (5–8 or 10–14 injections), and high ($\geq$10 or $\geq$15 injections) during the 12- and 24-month follow-up periods, respectively. Eyes with pre-existing glaucoma were identified at baseline.

Outcomes

The primary outcome was the adjusted mean change in IOP from baseline to 12 months using a regression model. Secondary outcomes were the proportion of eyes with clinically significant IOP elevation (defined as an IOP increase of at least 6 mmHg from baseline and resulting in an IOP of >21 mmHg in a single event) and predictors of change in IOP and rate of clinically significant IOP elevations during the 12- and 24-month follow-up (type of anti-VEGF agent, type of prefilled or nonprefilled ranibizumab, number of injections, initial diagnosis, and pre-existing glaucoma). Outcomes were analyzed by anti-VEGF agent, number of injections, prefilled or nonprefilled ranibizumab, and pre-existing glaucoma status groups as defined above.

Statistical Analysis

Descriptive data were summarized using the mean, standard deviation, median, first and third quartiles, and percentages where appropriate. Demographic characteristics were compared between anti-VEGF groups, prefilled groups, and glaucoma groups using the analysis of variance, Kruskal-Wallis test, *t* test, Wilcoxon rank-sum test, chi-square test, or Fisher exact test where appropriate. The mean changes in IOP between subgroups were compared using linear mixed-effects regression models. The proportion of eyes with a clinically significant elevation in IOP was analyzed using logistic mixed-effects regression. The main predictors investigated were type of anti-VEGF agents, type of ranibizumab prefilled or nonprefilled syringes, number of injections, initial diagnosis, and pre-existing glaucoma. Regression was adjusted for age, gender, baseline IOP, lens status, and cataract extraction during the follow-up as fixed effects and with nesting of outcomes within practitioners and patients with bilateral disease as random effects. Vitrectomy during the follow-up was not included in the model because of a very low incidence in our cohort. Because it was not mandatory to record IOP in the Fight Retinal Blindness! Registry, a possibility of bias existed as a result of selective reporting of IOP in

Table 1. Baseline Demographic Characteristics of Eyes Grouped by Type of Vascular Endothelial Growth Factor Inhibitor, Type of Syringe, and Pre-existing Glaucoma Status

Characteristic	Overall	Type of Anti–Vascular Endothelial Growth Factor Inhibitor			Type of Syringe*		Pre-existing Glaucoma Status	
		Bevacizumab	*Aflibercept*	*Ranibizumab*	*Prefilled*	*Nonprefilled*	*Present*	*Absent*
Eyes	3429	395	1138	1896	318	1104	184	3245
Patients	3032	380	1015	1688	293	990	177	2871
Females, no. (%)	1779 (58.7)	195 (51.3)	556 (54.8)	1064 (63)	199 (67.9)	617 (62.3)	98 (55.4)	1691 (58.9)
Age (yrs), mean (SD)	78.1 (10.4)	74.3 (11.2)	76.4 (11.1)	79.9 (9.4)	80.2 (10.3)	79.6 (8.7)	80.1 (9.1)	78 (10.4)
Intraocular pressure (mmHg), mean (SD)	14.4 (3.8)	14.9 (3.6)	14.4 (4.0)	14.4 (3.6)	13.5 (3.4)	14.8 (3.7)	15.2 (5.2)	14.4 (3.7)
Phakic lens status, no. (%)	2895 (84.4)	357 (90.4)	917 (80.6)	1621 (85.5)	230 (72.3)	1002 (90.8)	116 (63)	2779 (85.6)
Initial diagnosis, no. (%)								
Neovascular age-related macular degeneration	2901 (84.6)	284 (71.9)	898 (78.9)	1719 (90.7)	288 (90.6)	1026 (92.9)	132 (71.7)	2769 (85.3)
Diabetic macular edema	221 (6.4)	24 (6.1)	130 (11.4)	67 (3.5)	11 (3.5)	34 (3.1)	6 (3.3)	215 (6.6)
Macular edema secondary to RVO	307 (9.0)	87 (22.0)	110 (9.7)	110 (5.8)	19 (6)	44 (4)	46 (25.0)	261 (8.0)
History of glaucoma, no. (%)	184 (5.4)	12 (3.0)	70 (6.2)	102 (5.4)	18 (5.7)	61 (5.5)	184 (100.0)	0 (0)

RVO = retinal vein occlusion; SD = standard deviation.
*Cohort of eyes treated with ranibizumab: eyes initially treated from January 1, 2017, were defined as the prefilled syringe group and those initially treated before January 1, 2014, and January 1, 2013, were defined as the prefilled syringe group, thereby allowing 12 and 24 months of follow-up, respectively, before the start of prefilled packaging in January 2015.

high-risk patients. A sensitivity analysis was carried out on the cohort of eyes followed up by physicians who entered IOP measurement at least 50% of the time during follow-up visits.

A P value of 0.05 was considered statistically significant. P values from pairwise comparisons between anti-VEGF groups were adjusted for using the Holm-Bonferroni correction method. All analyses were conducted using R software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) with the glmmTMB package (version 0.2.3) for linear mixed-effects and generalized linear mixed-effects regression and the emmeans package (version 1.3.3) for pairwise comparison of adjusted means.

Results

Study Participants

A total of 3429 treatment-naïve eyes (395 receiving bevacizumab, 1138 receiving aflibercept, and 1896 receiving ranibizumab) from 3032 patients who received intravitreal monotherapy of VEGF inhibitors for neovascular AMD, DME, or ME secondary to RVO with 12 months of IOP follow-up data after starting treatment from December 1, 2013, through December 31, 2018, were identified (from an overall number of 10382 treatment-naïve eyes entered in the registry that received anti-VEGF injections from the selected countries involved in this study), of which 2125 (62%) had 24 months of follow-up data. The mean age overall was 78.1 years (standard deviation [SD], 10.4) years, and 58.7% of them were women. Two thousand nine hundred one eyes (84.6%) were treated for neovascular AMD, 221 eyes (6.4%) were treated for DME, and 307 eyes (9%) were treated for ME secondary to RVO. Table 1 summarizes the baseline characteristics in each of the groups. Eyes receiving ranibizumab were significantly older than those receiving aflibercept and bevacizumab (mean age, 74.3 years vs. 76.4 years vs. 79.9 years for bevacizumab, aflibercept, and ranibizumab, respectively; $P < 0.01$) and included a higher proportion of female patients (51.3% vs. 54.8% vs. 63.0% for bevacizumab, aflibercept, and ranibizumab, respectively; $P < 0.01$). The overall proportions of eyes in each group from the total number of injections received were 10.2% (350 eyes) and 8.2% (175 eyes) in the low number of injections group, 46% (1578 eyes) and 44.8% (951 eyes) in the medium number of injections group, and 43.8% (1501 eyes) and 47% (999 eyes) in the high number of injections group at 12 and 24 months of treatment, respectively. The proportion of eyes that underwent cataract surgery was 3.7% (107 eyes) and 6.3% (181 eyes) over 12 and 24 months of follow-up.

Intraocular Pressure Change Outcomes

Baseline mean IOP was 14.4 mmHg (SD, 3.8 mmHg) overall, 14.9 mmHg (SD, 3.6 mmHg) for bevacizumab, 14.4 mmHg (SD, 4.0 mmHg) for aflibercept, and 14.4 mmHg (SD, 3.6 mmHg) for ranibizumab. The overall mean IOP change at 12 and 24 months was −0.5 mmHg (95% CI, −0.6 to −0.3 mmHg; $P < 0.01$) and −0.4 mmHg (95% CI, −0.6 to −0.3 mmHg; $P < 0.01$), respectively. Figure 1 reports the adjusted mean IOP change at 12 and 24 months by type of VEGF inhibitor, number of injections, initial diagnosis, and pre-existing glaucoma status. Eyes receiving aflibercept showed significantly greater IOP reduction at 12 and 24 months

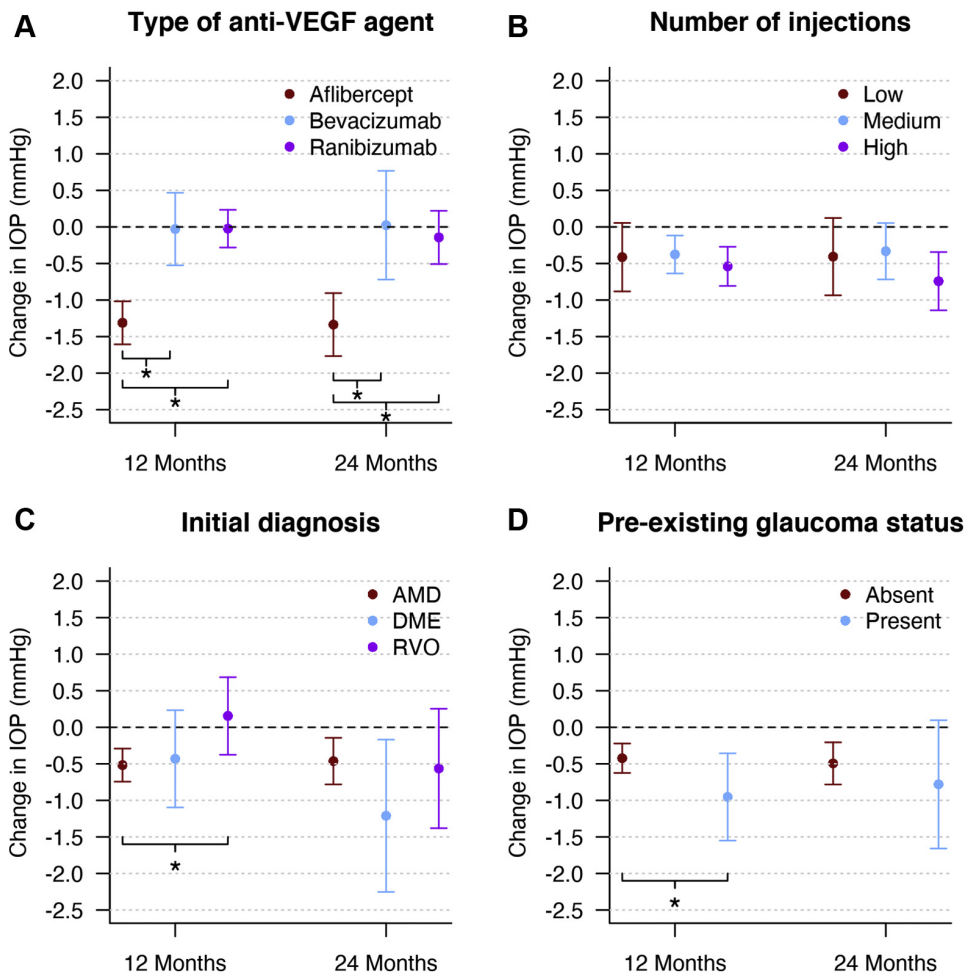

Figure 1. Graphs showing the adjusted change in intraocular pressure (IOP) from baseline until the 12- and 24-month follow-up visits by (**A**) type of vascular endothelial growth factor (VEGF) inhibitor, (**B**) number of injections, (**C**) initial diagnosis, and (**D**) pre-existing glaucoma status. AMD = age-related macular degeneration; DME = diabetic macular edema; RVO = retinal vein occlusion.

(adjusted mean, −1.3 mmHg [95% CI, −1.6 to −1.1 mmHg] and −1.3 mmHg [95% CI, −1.7 to −1.0 mmHg], respectively) than bevacizumab (adjusted mean, 0.0 mmHg [95% CI, −0.4 to 0.4 mmHg; $P < 0.01$] and 0.0 mmHg [95% CI, −0.6 to 0.6 mmHg; $P < 0.01$], respectively) and ranibizumab (adjusted mean, 0.0 mmHg [95% CI, −0.2 to 0.2 mmHg; $P < 0.01$] and −0.1 mmHg [95% CI, −0.4 to 0.2 mmHg; $P < 0.01$], respectively). No difference was found between bevacizumab and ranibizumab at 12 and 24 months. Also a significant trend was found for eyes with neovascular AMD (−0.5 mmHg [95% CI, −0.7 to 0.3 mmHg]) and pre-existing glaucoma (−1 mmHg [95% CI, −1.5 to 0.4 mmHg]) to be associated with a greater adjusted mean reduction in IOP at 12 months than eyes with RVO (+0.2 mmHg [95% CI, −0.3 to 0.6 mmHg]; $P = 0.010$) or pre-existing glaucoma (−0.4 mmHg [95% CI, −0.3 to 0.6 mmHg]; $P = 0.043$), respectively.

Clinically Significant Intraocular Pressure Elevation Outcomes

The overall proportion of clinically significant IOP elevations was 5.6% (193 eyes) at 12 months and 8.8% (186 eyes) at 24 months. Figure 2 describes the adjusted proportion of clinically significant IOP elevations during 12 and 24 months of follow-up by type of VEGF inhibitors, number of injections, initial diagnosis, and pre-existing glaucoma status. Clinically significant IOP elevations during 12 and 24 months of follow-up were less likely to occur in aflibercept-treated eyes (reference subgroup) than eyes treated with bevacizumab (odds ratio [OR], 2.2 [95% CI, 1.2−4.0; $P = 0.015$] and 2.7 [95% CI, 1.4−5.0; $P < 0.01$], respectively) or ranibizumab (OR, 2.8 [95% CI, 1.8−4.1; $P < 0.01$] and 2.6 [95% CI, 1.7−4.0; $P < 0.01$], respectively; Table 2). The rates of clinically significant elevated IOP were 2.4% and 3.9% in the aflibercept group, 5.2% and 9.7% in the bevacizumab group, and 6.4% and 9.4% in the ranibizumab group during 12 and 24 months of follow-up, respectively (Fig 2). Treated eyes with RVO tended to be significantly more at risk of IOP elevations during the first 12 months of follow-up than eyes treated for AMD (OR, 1.9 [95% CI, 1.1−3.1]; $P = 0.039$), although this association was not statistically significant at 24 months. Glaucomatous eyes were more likely to show an IOP elevation during both 12 and 24 months of follow-up (OR, 2.2 [95% CI, 1.2−3.8; $P = 0.012$] and

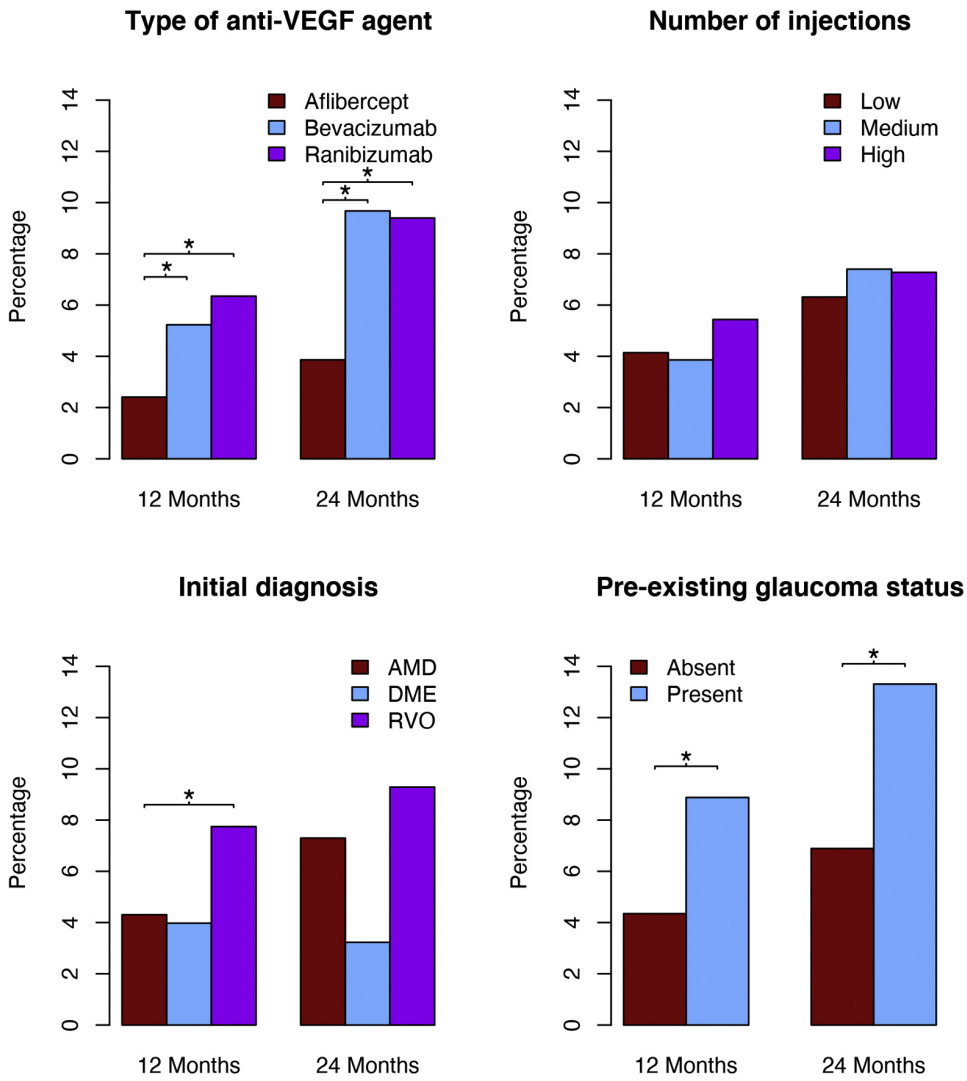

Figure 2. Bar graphs showing adjusted proportion of clinically significant intraocular pressure elevations during the 12- and 24-month follow-up by (**A**) type of vascular endothelial growth factor (VEGF) inhibitor, (**B**) number of injections, (**C**) initial diagnosis, and (**D**) pre-existing glaucoma status. AMD = age-related macular degeneration; DME = diabetic macular edema; RVO = retinal vein occlusion.

2.1 [95% CI, 1.1−3.8; $P = 0.025$], respectively) with an adjusted rate of 2.1% and 11.0% when treated with aflibercept, 14.1% and 23% when treated with bevacizumab, and 14.7% and 23.0% when treated with ranibizumab. A trend was found for an increasing rate of IOP elevations with more injections during both 1 and 2 years of follow-up; however, this was not statistically significant (Fig 2).

Intraocular Pressure Change Outcomes by Type of Ranibizumab Syringe

No statistically significant difference was found in the adjusted mean IOP change at 12 and 24 months between the 2 types of ranibizumab syringe (−0.1 mmHg [95% CI, −0.4 to 0.2 mmHg] and −0.2 mmHg [95% CI, −0.7 to 0.4 mmHg] for nonprefilled syringe vs. 0.1 mmHg [95% CI, −0.3 to 0.5 mmHg] and 0.7 mmHg [95% CI, −0.3 to 1.6 mmHg] for prefilled syringe; $P = 0.34$ and $P = 0.11$, respectively; Fig 3A, B). Nor did we find a significant association with the type of syringe and clinically significant IOP elevation (Table 2; Fig 3C). No significant variation was found at 12 and 24 months in the adjusted mean IOP change from baseline ($P = 0.39$ and $P = 0.87$, respectively) and rate of IOP elevations ($P = 0.81$ and $P = 0.75$, respectively) by year of treatment initiation.

Discussion

We used the Fight Retinal Blindness! Registry observational outcomes database to explore the effect of intravitreal VEGF inhibitors on long-term IOP change in treatment-naïve eyes for various exudative retinal diseases in routine clinical practice. The overall mean IOP at 12 and 24 months decreased slightly in our cohort, which corroborates recent

Table 2. Odds Ratios from Univariate and Multivariate Logistic Regression Analysis for Clinically Significant Intraocular Pressure Elevation at 12 and 24 Months

	Clinically Significant Intraocular Pressure Elevation							
	12 Months of Follow-up				*24 Months of Follow-up*			
	Univariate Analysis		**Multivariate Analysis**		**Univariate Analysis**		**Multivariate Analysis**	
Subgroup (Reference Subgroup)	*Odds Ratio (95% Confidence Interval)*	P *Value*	*Odds Ratio (95% Confidence Interval)*	P *Value*	*Odds Ratio (95% Confidence Interval)*	P *Value*	*Odds Ratio (95% Confidence Interval)*	P *Value*
By type of anti-VEGF drug (aflibercept)*								
Bevacizumab	2.37 (1.34–4.18)	**<0.01**	2.24 (1.24–4.04)	**<0.01**†	2.81 (1.54–5.12)	**<0.01**	2.66 (1.42–4.98)	**<0.01**‡
Ranibizumab	2.30 (1.56–3.39)		2.75 (1.82–4.14)		2.38 (1.57–3.60)		2.58 (1.68–3.96)	
By type of ranibizumab syringe (nonprefilled)‖								
Prefilled	0.76 (0.41–1.42)	0.39	0.93 (0.49–1.79)	0.83	0.61 (0.27–1.37)	0.23	0.79 (0.34–1.87)	0.60
By no. of injections (low)*								
Medium	0.83 (0.49–1.41)	0.07	0.93 (0.54–1.60)	0.09	0.99 (0.64–1.54)	0.95	1.19 (0.75–1.88)	0.75
High	1.21 (0.72–2.03)		1.33 (0.77–2.28)		1.05 (0.67–1.63)		1.16 (0.73–1.85)	
By initial diagnosis (neovascular AMD)*								
Diabetic macular edema	1.19 (0.65–2.19)	**<0.01**	0.92 (0.45–1.87)	**0.039**§	0.65 (0.28–1.54)	**0.034**	0.42 (0.16–1.11)	0.07
Macular edema secondary to RVO	2.39 (1.53–3.74)		1.86 (1.13–3.09)		1.85 (1.11–3.09)		1.30 (0.73–2.31)	
By pre-existing glaucoma status (absent)*								
Glaucoma	2.25 (1.34–3.78)	**<0.01**	2.15 (1.23–3.75)	**0.012**	2.21 (1.26–3.88)	**<0.01**	2.07 (1.13–3.81)	**0.025**

AMD = age-related macular degeneration; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.
Number of injections groups were defined as low if 3 to 4 injections were administered during the first year or 3 to 9 injections were administered during 2 years of follow-up, as medium if 5 to 8 injections were administered during first year or 10 to 14 injections were administered during 2 years of follow-up, and high if at least 10 injections were administered during the first year or at least 15 injections were administered during 2 years of follow-up.
*Multivariate model included type of anti-VEGF agent, age, gender, lens status, cataract extraction during the follow-up, baseline intraocular pressure, frequency of injection, and history of glaucoma.
†Pairwise comparison with Holm-Bonferroni adjustment for multiple comparisons: aflibercept vs. bevacizumab ($P = 0.015$), aflibercept vs. ranibizumab ($P < 0.01$), and bevacizumab vs. ranibizumab ($P = 0.44$).
‡Pairwise comparison with Holm-Bonferroni adjustment for multiple comparisons: aflibercept vs. bevacizumab ($P < 0.01$), aflibercept vs. ranibizumab ($P < 0.01$), and bevacizumab vs. ranibizumab ($P = 0.91$).
‖Multivariate model included type of ranibizumab syringe, age, gender, lens status, cataract extraction during the follow-up, baseline intraocular pressure, frequency of injection, and history of glaucoma.
§Pairwise comparison with Holm-Bonferroni adjustment for multiple comparisons: neovascular AMD vs. diabetic macular edema ($P = 0.82$), neovascular AMD vs. RVO ($P = 0.046$), and diabetic macular edema vs. RVO ($P = 0.13$).

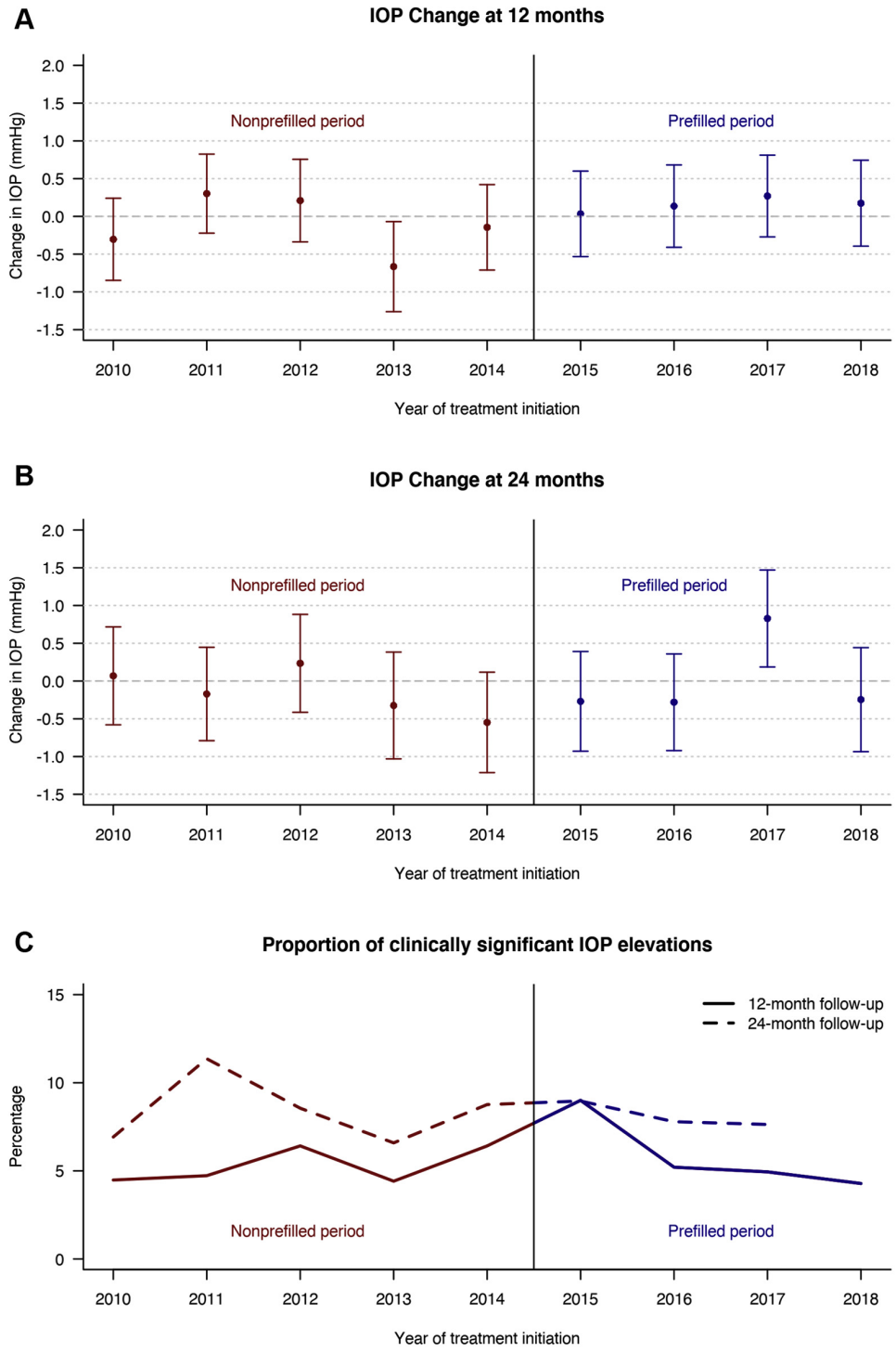

Figure 3. Graphs showing adjusted change in intraocular pressure from (**A** and **B**) baseline and (**C**) adjusted proportion of clinically significant intraocular pressure elevations by year of treatment initiation at 12 and 24 months for eyes treated with ranibizumab.

results.[4,8] Interestingly, eyes treated with aflibercept showed significantly greater adjusted mean reduction in IOP than bevacizumab and ranibizumab at 12 and 24 months. This finding was reported previously in a secondary analysis of intraocular pressure outcomes in the VIEW 1 and 2 study that compared aflibercept (2 mg monthly, 2 mg every 2 months after 3 initial monthly doses, and 0.5 mg monthly) with ranibizumab (0.3 mg monthly) for neovascular

AMD.[5] The statistically significant difference seen in our study is minor and may not be clinically relevant.

The outcomes of clinically significant IOP elevation (increase of at least 6 mmHg from baseline and resulting in an IOP of more than 21 mmHg in a single event) are of more clinical interest. Our overall rate of 5.6% at 12 months is higher than the 2.8% rate of elevated IOP of the Intelligent Research in Sight Registry study[4] and the 3.4% rate of elevated IOP by the study of Adelman et al.[7] This difference may be explained by the stricter definition of IOP elevation (proportion of eyes with a baseline IOP of $\leq$21 mmHg that showed an IOP rise of at least 6 mmHg that resulted in an IOP of more than 21 mmHg at 2 consecutive visits) for the former study and the exclusion of glaucoma patients at baseline for the latter, who are possibly more at risk of IOP elevations. An exploratory ad hoc analysis of Diabetic Retinopathy Clinical Research Network studies assessing IOP change between ranibizumab and focal or grid laser therapy for DME through 3 years found similar rates of IOP elevations with 5.7% at 1 year and a cumulative incidence of 9.5% at 3 years in the ranibizumab group, although their definition also was different (same criteria at 2 consecutive visits or initiation or augmentation of IOP-lowering drug). The rate of elevated IOP reported in VIEW 1 and 2, defined as IOP of more than 21 mmHg at 2 consecutive visits, was in keeping with our results, with 5.2% versus 2.5% versus 2.4% versus 1.5% at 1 year and 8.4% versus 3.2% versus 4.2% versus 2.7% at 2 years for ranibizumab, aflibercept 2 mg monthly, aflibercept 2 mg every 2 months after 3 initial monthly doses, and aflibercept 0.5 mg monthly, respectively.[5]

The pathophysiologic process underlying sustained IOP elevations after treatment with VEGF inhibitors has not been identified, although several causes have been proposed. It may be related to a decrease in aqueous outflow by chronic mechanical damage to the trabecular meshwork resulting from repeated injection-related IOP spikes, direct toxicity of VEGF inhibitors itself, obstruction resulting from accumulation of protein aggregates or silicone droplets, or even trabecular meshwork constriction mediated by inhibition of nitric oxide synthesis.[6,12–14]

We found that aflibercept-treated eyes consistently were less likely to show IOP elevations than bevacizumab- and ranibizumab-treated eyes during the follow-up, which is consistent with the analyses in VIEW 1 and 2.[5] Freund et al[5] proposed that accumulation of protein aggregates may be greater with ranibizumab compared with aflibercept or that repeated ranibizumab injections lead to progressive trabeculitis secondary to an endotoxin inflammatory response caused by a different manufacturing process involving *Escherichia coli* bacteria compared with Chinese hamster ovary cells for aflibercept. However, bevacizumab is produced with a similar production processes as aflibercept, and we found a similar consistent rate of IOP elevations between bevacizumab and ranibizumab, which does not support this theory. Ranibizumab and bevacizumab bind to all VEGF-A isoforms, whereas aflibercept can trap VEGF-A, VEGF-B, and placental growth factor (PlGF).[15] Placental growth factor acts only on pathologic angiogenesis and inflammation and is not involved in physiologic angiogenic processes.[16–18] Anti–vascular endothelial growth factor agents may lead to drug resistance resulting from an angiogenic rescue program with upregulation of other growth factors such as PlGF.[17–19] Repeated injections of ranibizumab and bevacizumab may induce a progressive inflammatory response secondary to upregulation of intraocular PlGF levels, which makes those eyes more at risk of inflammatory-related IOP elevations than eyes treated with aflibercept, which possibly controls this deleterious upregulation.

No previous studies in the literature have assessed the impact of syringe packaging on IOP outcomes. Our study tried to address this question with a subanalysis of the ranibizumab cohort. Our examination found no significant difference in IOP outcomes between the prefilled and nonprefilled syringe period. This is not consistent with the theory that droplets of silicone oil, applied to lubricate the components of insulin syringe used for bevacizumab or nonprefilled ranibizumab packing, play a role in IOP elevations.[12,14] This finding needs to be confirmed in further studies.

It has been reported that increased frequency and number of injections may raise the risk of IOP elevations.[4,20,21] A trend was found for an increasing rate of elevated IOP with a higher number of injections in the present study, although this was not statistically significant; reports on this topic are conflicting.[22,23]

Eyes with pre-existing glaucoma were more at risk of clinically significant IOP elevation during the follow-up, which is also consistent with previous reports.[4,24,25] Bergen et al[17] recently reported that PlGF aqueous levels were elevated in glaucomatous patients. The consistently increased rate of IOP elevations in bevacizumab- and ranibizumab-treated eyes compared with aflibercept-treated eyes in the glaucomatous subgroup emphasizes a possible involvement of PlGF in the pathophysiologic features of IOP elevation in eyes treated with VEGF inhibitors.

This study has several strengths and limitations. Observational studies provide data that represent the ability of a drug to achieve its intended purpose in the real world. Our data are representative of a wide variety of real-world international practices. Although variability exists in the quality of data in observational studies, the Fight Retinal Blindness! Registry system includes quality assurance measures that eliminate out-of-range and missing data.[10] Well-designed observational studies may not overestimate the effect of treatment systematically as randomized clinical trials may do.[26] The limitations of the study are, first, that no specific protocol for IOP measurements was defined, so variability may exist in methodology, frequency, and timing of IOP measurements between practitioners and over time. We did not record which instrument was used to record the IOP, so we were unable to adjust for this in our analysis. We included nesting of outcomes within practitioners in our models to help control for these effects, but there may still be biases, particularly if practitioners used different instruments within the same clinic. We also performed a sensitivity analysis on the

cohort of eyes followed up by physicians who entered IOP measurements at 50% or more follow-up visits to account for possible bias caused by doctors who may enter IOP measurements only for at-risk patients. This did not modify the main findings of the primary analysis (see Supplemental Material, available at www.aaojournal.org). Second, the baseline diagnosis of glaucoma may vary among practitioners; however, our data are consistent with previous reports showing that eyes with pre-existing glaucoma are more at risk of IOP elevations.[4] Third, pseudophakic status at baseline may have been underreported because the rate reported seemed to be relatively low. We have attempted to control for the influence of lens status on IOP outcomes by adjusting the statistical analysis for baseline lens status and cataract extraction during the follow-up. Fourth, data on baseline subtype and severity of glaucoma and management of elevated IOP during follow-up, such as addition or introduction of IOP-lowering drops, laser therapy, or incisional glaucoma surgery, were not monitored. We were unable to address the influence of these factors on the results. Fifth, the definition of clinically significant IOP elevation was based on a single event. Although it may have overestimated the results, we preferred a single-event definition because of the absence of data on glaucoma treatment during follow-up. Sixth, we did not assess the influence of IOP change outcomes on the onset of glaucoma and the anatomic and functional progression of glaucoma. Seventh, we were not able to include fellow-eye data as a control for our results. Fellow eyes have a basic rate of IOP rises.[4,8] However, our results are in keeping with the literature, and the absence of a control does not influence our finding regarding predictors of IOP changes and elevations.

In conclusion, our study found that aflibercept reduces IOP slightly from baseline to 12 and 24 months compared with bevacizumab and ranibizumab, although this difference was not clinically significant. Of more clinical interest, clinically significant IOP elevations occurred in a small proportion of eyes receiving VEGF inhibitors. Aflibercept was associated with fewer clinically significant IOP elevations, whereas eyes with pre-existing glaucoma were at a higher risk. Aflibercept may be safer than bevacizumab or ranibizumab in eyes with glaucomatous optic neuropathy or ocular hypertension that develop into exudative retinal disease.

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