Long Term Outcomes for Patients Treated with Intra-vitreal Anti-VEGF or Steroid Injections for Macular Oedema Secondary to Retinal Vein Occlusion

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ABSTRACT

This systematic review assessed the long-term outcomes for patients treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) or steroids for macular oedema (MO) secondary to retinal vein occlusion (RVO). The aim was to answer patients' questions on the long-term outcomes of these treatments. Studies investigating patients of all ages with MO due to RVO only were included. Inclusion of comparative and non-comparative studies ensured use of real-world evidence. The outcomes of interest were best corrected visual acuity (BCVA) and central retinal thickness (CRT) therefore, studies that investigated BCVA and/or CRT at minimum two years were accepted. Studies that recorded change in BCVA or CRT were excluded as were studies not written in English. Four databases were searched on 22nd July 2021: Ovid Embase, Ovid Medline, Web of Science and the Cochrane library. Risk of bias was assessed using separate tools for each study type. Data was synthesised using SPSSv27. In total, 48 studies were included, comprising 10775 participants. Studies with separate data for either RVO type or treatment were analysed as separate entities which led to 76 data sets being included. There were 34 studies analysing CRVO or BRVO separately and eight studies with combined data. Retrospective case series studies were the most abundant, 30 in total, followed by 28 cohort studies, 15 RCTs and three prospective case series. The mean age of participants was 67.1 years (SD 3.6), and the mean percentage of males was 52.0% (SD 9.3). Ranibizumab treatment was most common followed by combination treatment, used in 28 and 26 studies respectively. Overall, mean BCVA improved by 16.1 letters five years after initial treatment, from 51.6 (SD 11.5) baseline. Patients with CRVO and BRVO improved at two years, by 9.1 and 10.9 letters respectively, this difference at two years was significant (p=0.035). At five years, BRVO patients improved by 16.2 letters compared to 15.6 letters in CRVO patients; this difference between RVO types was significant (p=0.003). In patients treated with ranibizumab, the largest long-term improvement in BCVA was 11.2 letters after three years, compared to bevacizumab or dexamethasone patients who achieved a decrease in BCVA of 2.4 letters and increase of 6.3 letters respectively. Anatomical outcomes also improved over five years; mean CRT decreased by 222.5µm when analysing all 76 data sets. Patients given combination treatment achieved a 179.4µm decrease in CRT at four years, compared to a 291.1µm decrease in ranibizumab patients. The limitations of this study included a lack of BCVA data for dexamethasone, aflibercept, bevacizumab and triamcinolone treatment types beyond three years, making direct comparisons difficult. Three studies were deemed to have a high risk of bias and 11 studies with moderate risk of bias. The high heterogeneity of study types and outcomes was a strength of this study, allowing for real-world results to be analysed. In conclusion, these results suggest benefit from receiving long-term intravitreal treatments for MO due to RVO and equip clinicians with long-term evidence to advise and reassure patients of positive long-term visual and anatomical outcomes with these drugs.

Keywords: macular oedema; retinal vein occlusion; anti-VEGF; steroid; long-term; ophthalmology; best corrected visual acuity; central retinal thickness

INTRODUCTION

How life is experienced depends on the health of our eyes (Brown, 1999). Vision is an important gift allowing people to interpret and to react to many different situations. Sight is the most dominant of senses and the eye is estimated to perceive 80% of the world around us (WHO, 2021). It is important for good quality of life (QOL) and overall health.

Sight is mediated through the retina, which allows high-definition images to be produced in the brain provided each of the ten retinal layers are intact. The inner retina has a rich vascular supply formed by the retinal artery, originating from the ophthalmic artery which is a branch of the internal carotid artery. It is drained by the retinal veins. The macula spans 5 mm diameter, located at the centre of the retina and is responsible for central and much of colour vision.

Retinal vein occlusion (RVO) is the second most common retinal cause of vision loss after diabetic retinopathy, making it necessary to treat and manage to ensure good vision outcomes for those affected. In 2019, a global prevalence of RVO was estimated at 0.77% in adults aged 30-89 years and an age-related increase in prevalence of RVO from 0.23% in people aged 30-39 years to 2.64% in those aged 80-89 years (Song et al., 2019).

Retinal vein occlusion is caused by thrombus formation arising from external pressure from an adjacent arteriosclerotic artery sharing a common adventitial sheath (RCOphth, 2015). There are several common risk factors implicated in RVO, including hypertension, diabetes and hyperlipidaemia. In the younger population of patients with RVO, there are several other risk factors including blood coagulation disorders such as myeloma or leukaemia and systemic inflammatory disorders such as sarcoidosis. The two main consequences of RVO are the development of macular oedema and neovascularisation of the iris or retina.

One study reported significantly lower QOL in patients with central retinal vein occlusion (CRVO) than in the unaffected control group, even when vision was good in the unaffected eye, highlighting the importance of effectively treating this condition (Awdeh et al., 2010).

Macular oedema (MO) affects 75% of patients with branch retinal vein occlusion (BRVO) and 85% patients with (CRVO) in England and Wales and is the commonest cause of visual loss in RVO (RCOphth, 2015).

Macular oedema secondary to RVO occurs due to increased hydrostatic pressure, inflammatory cytokines and increased capillary permeability causing leakage into the extracellular space (Noma, Yasuda and Shimura, 2020). Vascular endothelial growth factor (VEGF) is the key cytokine mediating capillary leakage and subsequent MO and can therefore be targeted by several therapies including bevacizumab, ranibizumab and aflibercept, called anti-VEGF medications. Other intravitreal treatment options include dexamethasone and triamcinolone which are steroid therapies (RCOphth, 2015).

Intra-vitreal injections allow insertion of medication into the vitreous cavity to allow the treatment to target the retina and are used in a number of eye conditions, including MO (Yorston, 2014). The patient is conscious throughout the procedure as the eye is sterilised thoroughly using strict aseptic technique before it is anaesthetised and the treatment injection is given.

Although the short term outcomes of these treatments are well described in the literature, the long term efficacy and outcome of intravitreal injections is less well established for patients with MO caused by RVO. Although several landmark studies have looked at short term outcomes for CRVO such as the CRUISE, COPERNICUS and GALILEO trials, the follow up time was only 52, 100 and 76 weeks respectively (Rubio and Genentech, 2011; Pielen et al., 2017). The BRAVO and VIBRANT trials studied anti-VEGF efficacy in patients with BRVO for 52 and 24 weeks respectively (Campochiaro et al., 2010b; Campochiaro et al., 2015). The GENEVA study investigated efficacy of dexamethasone on patients with CRVO or BRVO for 24 weeks (Haller et al., 2010). Anecdotally, clinicans report that patients want to know their long term visual prospects and an evidence based, comprehensive answer is lacking. Therefore, this systematic review aims to evaluate treatment outcomes assessed after a minimum of two years from first intravitreal injection for patients with MO caused by RVO, and should equip clinicians and patients with a better understanding of the long term effectiveness of anti-VEGF and steroid medications.

METHODS

This was a scoping systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines were used to direct the conduct and report of this review (Page et al., 2021).

Eligibility Criteria

Studies on people of all ages and ethnicities undergoing intravitreal injections for the treatment of MO due to RVO were included. It was planned to accept comparative and non-comparative studies and also retrospective and prospective studies. Although randomised controlled trials (RCTs) are the gold standard practice, cohort and retrospective case series studies were also included to represent 'real world' results.

The outcomes of interest were best corrected visual acuity (BCVA), central retinal thickness (CRT) in μm, and

QOL, each captured two or more years after primary initiation of treatment. Anti-VEGF and steroid intravitreal treatments used to treat MO secondary to RVO were included to avoid constrictiveness. Eligible trials had to include data with at least a two-year follow up or continued therapy; therefore, trials of less than this timeframe were excluded. Studies using laser treatment as the comparator arm were also excluded.

Information Sources & Search Strategy

An electronic search using relevant search terms was conducted in the Medline, Embase, Cochrane and Web of Science databases to identify potentially eligible publications. The four databases were used to ensure comprehensiveness of the review and to reduce the risk of missing a potentially eligible study. These searches were conducted on the 14th June 2021 and last consulted on 22nd July 2021. Search filters used included English language studies only, to ensure timely completion of the review. No time limits were set on publication dates to ensure comprehensiveness of the search.

Selection Process & Data Collection

The first step in identifying studies for analysis involved establishing the search terms. It was planned to informally trial search strategies before selecting appropriate search terms. This was achieved by assessing which search strategy yielded sufficient coverage without creating excess results. The search strategies used are summarised in Table 1 and Table 2. The next step involved applying the selected search terms to each of the four databases, ensuring identical methodology was used to maintain consistency. This created a list of potentially eligible publications.

TABLE 1. Search concepts for search one

	$Population_1$	$Population_2$	Intervention
OR	Macular oedema	Retina* vein occlusion	Intravitreal injection*
OR	Macular edema	Retinal vein blockage	Intravitreal treatment*
OR		Retinal venous occlusion	Intravitreal drug administration
OR		Retinal venous blockage	Intravitreal
		Retinal disease*	
	AND	*AND*	*AND*

$Population_1$ = Patients with macular oedema.
$Population_2$ = Patients with retinal vein occlusion.

TABLE 2. Additional search concepts for search two

	Intervention
OR	Bevacizumab
OR	Aflibercept
OR	Ranibizumab
OR	Dexamethasone
OR	Triamcinolone
OR	Steroid
	AND

Each record was screened independently, looking at titles and abstracts of the potentially eligible list to exclude publications that were obviously ineligible. If unclear, studies were included at this stage to avoid excluding an eligible study. EndNote software was used to identify duplicates between databases before manually filtering sources for appropriate timeframe, study type, treatment type and condition. Once this was complete, the list was examined again in more detail, assessing full text sources if necessary to clarify and produce a list of 'definitely eligible' studies. This list was then analysed for data extraction.

Data Items

The aim was to investigate the long-term outcomes for patients with MO due to RVO, treated with a) intravitreal anti-VEGF injections specifically: aflibercept, bevacizumab or ranibizumab; or b) intravitreal steroid injections including dexamethasone or triamcinolone; or c) any combination of these therapies, described as 'combination treatment' throughout this review. Long-term was defined as outcomes assessed at two years or longer, up to five years.

Publications were categorised as 'unsure' if the abstract was not comprehensive enough to decide on eligibility and full text was not available. An inter-library loan was then requested. The full text of each 'definitely eligible' publication was read to extract specific variables when available. These variables included: patient age, the mean, median and range, the percentage male within each study, country of study and ethnicity of participants. The baseline BCVA was recorded as well as the subsequent BCVA, if available, at two years, three years, four years and five years after initiation of treatment. The baseline CRT was also recorded and if available, the subsequent CRT was also recorded annually up to five years. The study design was noted as well as the database from which the publication was sourced. The baseline and subsequent annual intraocular pressure and QOL scores were also recorded.

Study Risk of Bias Assessment

The study level risk of bias was assessed using the Cochrane Risk of Bias Tool (Sterne et al., 2019) for

included RCTs. Cohort studies were assessed using The Critical Appraisal Skills Programme cohort checklist (CASP, 2018) and retrospective case studies were assessed using The Joanna Briggs Institute (JBI) Critical Appraisal case series checklist (Munn Z et al., 2020). Studies included were categorised into low risk, high risk or unclear categories based on selection, detection, attrition and reporting bias domains. Selection bias occurs when there are differences between baseline characteristics of the comparison groups. Detection bias occurs when outcomes are determined differently between comparison groups. Attrition bias describes the systematic differences that occur between comparison groups due to withdrawal of participants from studies (Higgins et al., 2011). If information needed to judge the risk of bias was lacking, studies were classified as 'unclear risk of bias'. The overall risk of bias was colour coded in a table included in the results section.

Synthesis Methods

Study characteristics were inserted into an Excel table, with BCVA or CRT values recorded at baseline and at two years as essential inclusion criteria. Missing data was recorded as '999' on the Excel table. Any BCVA values recorded in the log[MAR] scale or Snellen chart were converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letters manually using a conversion table, and the percentage of males was calculated manually based on participant numbers and gender specified. The country of study, RVO type, treatment used, BCVA method, type of study, database and publication type were coded in an Excel table and a corresponding key written.

All outcomes and study characteristics were recorded on one Excel table according to the author's name and year of study. Once recorded, data was synthesised using SPSSv27. The mean, standard deviation, range and 95% confidence intervals were recorded for baseline BCVA and corresponding BCVA at two years, three years, four years, and five years respectively for each RVO type, treatment used and study type, divided into RCTs and 'other' study types. The mean, standard deviation, range and 95% confidence intervals were also recorded for baseline CRT and corresponding CRT at two years, three years, four years, and five years respectively for each RVO type, treatment used and study type, divided into RCTs and 'other' study types. The means for BCVA and CRT were compared independently using Independent Sample's T-Test for comparing two groups and one-way ANOVA test for comparing greater than two groups. The significance value was set at $p<0.05$.

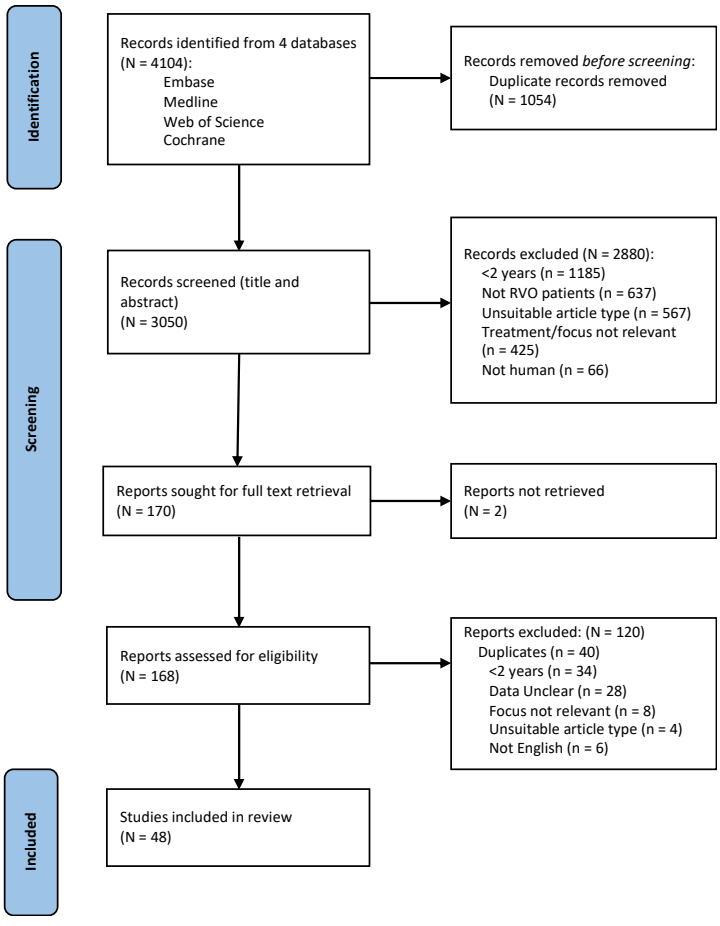

Figure 1. Flowchart of selection and screening process. Adapted from (Page et al., 2021).

RESULTS

Study Characteristics

The search strategy identified 4104 potentially eligible studies from four databases: Ovid Embase, Ovid Medline, Cochrane library and Web of Science. Using Endnote's automation tool, 1054 duplicates were identified and removed. This left 3050 studies which were screened using the title and abstracts. If unsure of eligibility, the study was kept for assessment using the full text. In total, 2880 studies were excluded at this stage; 38.9% of excluded studies had a follow up time less than two years. This number included studies with a two-year mean follow up but range starting less than two years. Studies focusing on conditions other than MO due to RVO or treatments other than those mentioned previously were also excluded. Once screening using title and abstract was complete, 170 studies were left to screen using full text if available. Two studies had no full text available, leaving 168 studies to be screened. In total, a further 120 were excluded for reasons which included the follow up time totalling less than two years (or <100 weeks if studies started at zero weeks). Studies were also excluded if absolute BCVA or CRT values were not available or if full text was not available in English. Other studies focused on outcomes not relevant to this review, and were therefore excluded. Overall, 48 studies were eligible for analysis. This process is illustrated in Figure 1.

If articles investigated patients with both CRVO and BRVO with separate outcomes, these studies were analysed separately, based on condition, as well as different drug regimens; this increased the effective study number to 76 in total. Eight studies included both RVO types, however, did not present data separately; therefore, these were recorded as one study with 'mixed' RVO type recorded. Eight studies separated RVO type into ischemic and non-ischemic (Korobelnik et al., 2016), however this was ignored due to the small numbers of results and inconsistent categorisation of retinal ischemia which would limit conclusions. The main study characteristics of the included studies are summarised in Table 3 and Table 4. The study types were categorised according to the original author's categorisation. For analysis, studies were grouped into RCT and non-RCT categories. Non-RCT studies included: prospective case series, retrospective case series and cohort studies. Randomised controlled trials were defined by the original author in the study design.

TABLE 3. Study characteristics (n = 76)

Features	Number of Data Sets
RVO Type	
CRVO	34
BRVO	34
CRVO/BRVO	8
Missing	0
Treatment Used	
Dexamethasone	8
Aflibercept	5
Bevacizumab	8
Ranibizumab	28
Triamcinolone	1
Combination Treatment	26
Missing	0
Study Type	
Cohort	28
RCT	15
Retrospective case series	30
Prospective case series	3
Missing	0
Mean Age / Years	
50-60	4
60-70	49
70-80	14
Missing	9
Country of Study	
UK	11
USA	27
Germany	7
Greece	5
Japan	5
Other	20
Missing	1
% Male	
20-40	5
40-50	17
50-60	31
>60	11
Missing	12

TABLE 4. Main Features of the Included Articles in this Review (n= 48)

Study author & year	Participants (n)	Study type	RVO type	Drug regimen	Study outcomes	Conclusions
(Abdallah et al., 2019)	9	Retrospective case series	Separate CRVO & BRVO data	Dexamethasone	BCVA & CRT at 3 years	No significant vision gains with dexamethasone.
(Bajric & Bakri, 2016)	5	Retrospective case series	CRVO only	Combination	BCVA & CRT at 2, 3 & 4 years	BCVA & CRT improvement maintained at four years.
(Blanc et al., 2018)	66	Retrospective case series	Mixed	Dexamethasone & combination	BCVA & CRT at 2 & 3 years	Dexamethasone effective at 3 years.
(Blin et al., 2018)	301	Cohort	Separate CRVO & BRVO data	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab effective at 2 years.
(Brown et al., 2014)	15	Cohort	CRVO only	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab improved vision.
(Busch et al., 2019)	155	Retrospective case series	Separate CRVO & BRVO data	Combination	BCVA & CRT at 2 & 3 years	Early treatment improved final outcomes.
(Calugaru & Calugaru, 2015)	57	Cohort	CRVO only	Bevacizumab	BCVA & CRT at 3 years	Bevacizumab improved vision at 3 years.
(Campochiaro et al., 2010a)	40	RCT	Separate CRVO & BRVO data	Combination	BCVA & CRT at 2 years	Long term visual improvement with anti-VEGF.
(Campochiaro et al., 2014)	66	Cohort	Separate CRVO & BRVO data	Ranibizumab	BCVA & CRT at 2, 3 & 4 years	Ranibizumab improves long term visual outcomes.
(Chatziralli et al., 2017)	15	Retrospective case series	CRVO only	Combination	BCVA & CRT at 2 years	Anti-VEGF is effective for MO due to RVO.
(Chatziralli et al., 2018)	54	Retrospective case series	Separate CRVO & BRVO data	Ranibizumab	BCVA & CRT at 2, 3 & 4 years	Ranibizumab is effective long term.
(Chittajallu & Prakash, 2018)	101	Retrospective case series	BRVO only	Ranibizumab	BCVA at 2 years	Long term ranibizumab is effective.
(Costa et al., 2021)	208	Retrospective case series	Mixed	Dexamethasone & combination	BCVA & CRT at 3 years	Intravitreal treatment improved long term outcomes.
(Farinha et al., 2015)	32	Retrospective case series	Separate CRVO & BRVO data	Ranibizumab	BCVA & CRT at 2 & 3 years	Ranibizumab was satisfactory long term.
(Gale et al., 2020)	4879	Retrospective case series	CRVO only	Ranibizumab, dexamethasone & combination	BCVA at 2 & 3 years	Better visual outcomes with ranibizumab than other treatments.
(Guichard et al., 2018)	76	Retrospective case series	Mixed	Ranibizumab	BCVA & CRT at 2 years	Treat & extend superior to PRN for MO due to RVO.
(Heier et al., 2012)	203	RCT	Separate CRVO & BRVO data	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab is safe & effective.
(Heier et al., 2014)	114	RCT	CRVO only	Aflibercept	BCVA & CRT at 2 years	Anatomical improvements reduced between weeks 52 & 100.
(Hikichi et al., 2014)	89	Cohort	BRVO only	Bevacizumab	BCVA & CRT at 2 years	Bevacizumab is beneficial at 2 years
(Horner et al., 2020)	54	Cohort	Separate CRVO & BRVO data	Ranibizumab & combination	BCVA & CRT at 2 & 3 years	Combination therapy effective for MO due to RVO.
(Hosogi et al., 2019)	32	Retrospective case series	BRVO only	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab effective for BRVO patients.
(Hykin et al., 2019)	463	RCT	CRVO only	Ranibizumab, aflibercept & bevacizumab	BCVA & CRT at 2 years	Aflibercept was non-inferior to ranibizumab.
(Iftikhar et al., 2019)	90	Prospective case series	Separate CRVO & BRVO data	Combination	BCVA & CRT at 2, 3, 4 & 5 years	Sustained anti-VEGF improved visual & anatomical outcomes.
(Inagaki et al., 2019)	20	Cohort	BRVO only	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab improved vision at 2 years.

Continues

TABLE 4. Continued

Study author & year	Participants (n)	Study type	RVO type	Drug regimen	Study outcomes	Conclusions
(Khurana et al., 2019)	16	Cohort	CRVO only	Aflibercept	BCVA & CRT at 2 years	Aflibercept provided improvement at 2 years
(Korobelnik et al., 2016)	375	Cohort	Separate CRVO & BRVO data	Dexamethasone	BCVA & CRT at 2 years	Dexamethasone implant is safe
(Larsen et al., 2018)	357	Cohort	CRVO only	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab is effective at 2 years
(Lee, Jung & Sohn, 2014)	453	Cohort	BRVO only	Triamcinolone, bevacizumab & combination	BCVA at 2 years	Anti-VEGF provides improved BCVA at 2 years.
(Lida-Miwa et al., 2019)	58	Prospective case series	BRVO only	Ranibizumab	BCVA & CRT at 2 years	Neovascular changes present in BRVO treated with ranibizumab.
(Lo et al., 2020)	214	Retrospective case series	Mixed	Combination	BCVA & CRT at 2 years	Early BCVA & CRT improvements may predict long-term outcomes.
(Lo et al., 2021)	214	Retrospective case series	Separate CRVO & BRVO data	Combination	BCVA & CRT at 2 years	Early anatomic response increases chance of treatment cessation.
(Loukiano et al., 2016)	33	Cohort	Separate CRVO & BRVO data	Bevacizumab	BCVA & CRT at 2 years	Bevacizumab provides long term BCVA improvement.
(Maggio et al., 2020)	223	Cohort	Separate CRVO & BRVO data	Combination	BCVA & CRT at 2, 3, 4 & 5 years	Ranibizumab & dexamethasone effective long term.
(Mansour et al., 2018)	10	Cohort	Mixed	Aflibercept	BCVA at 2 years	BCVA improves over 2 years with aflibercept.
(McAllister et al., 2018)	29	RCT	CRVO only	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab effective in CRVO patients.
(Ozkaya, Tarakcioglu & Tanir, 2018)	174	Retrospective case series	BRVO only	Ranibizumab & dexamethasone	BCVA & CRT at 2 years	Ranibizumab & dexamethasone effective in BRVO.
(Risard et al., 2011)	20	Cohort	CRVO only	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab improves visual & anatomical outcomes.
(Sakanishi et al., 2021)	40	Cohort	BRVO only	Aflibercept	BCVA & CRT at 2 years	Aflibercept effective at 2 years for BRVO .
(Scott et al., 2011)	389	RCT	Separate CRVO & BRVO data	Combination	BCVA & CRT at 2 years	Younger age predictive of higher BCVA.
(Sen et al., 2021)	267	RCT	CRVO only	Combination	BCVA at 2 years	HIgher baseline BCVA was predictive of better BCVA outcomes.
(Sophie et al., 2013)	21	Retrospective case series	Separate CRVO & BRVO data	Ranibizumab	BCVA at 2 years	Infrequent ranibizumab not sufficient to treat MO due to RVO.
(Sophie et al., 2019)	205	RCT	BRVO only	Ranibizumab	BCVA & CRT at 2 years	Perfusion maintenance crucial for good outcomes in CRVO.
(Spooner et al., 2019)	68	Retrospective case series	Separate CRVO & BRVO data	Combination	BCVA & CRT at 5 years	Anti-VEGF achieved good long term outcomes for RVO.
(Stredova et al., 2019)	39	Cohort	BRVO only	Ranibizumab	BCVA & CRT at 2 years	Ranibizumab improved long term outcomes for BRVO.
(Tadayoni et al., 2017)	183	RCT	BRVO only	Ranibizumab	BCVA & CRT at 2 years	Long term efficacy & safety of ranibizumab proven.
(Tsagkataki et al., 2015)	35	Retrospective case series	BRVO only	Bevacizumab	BCVA & CRT at 2 years	Bevacizumab provided resolution of MO in one third of patients.
(Volkmann et al., 2020)	16	Cohort	Mixed	Combination	BCVA at 2 years	BCVA improves with anti-VEGF.
(Wu et al., 2009)	63	Cohort	BRVO only	Bevacizumab	BCVA & CRT at 2 years	Bevacizumab is effective at 2 years.

Risk of Bias

Table 5 represents the overall risk of bias for each included study, grouped according to study type. The complete risk of bias assessments are found in Appendix A, B and C.

TABLE 5. Overall Risk of Bias for RCTs, Cohort Studies and Case Series

RCT - Cochrane Risk of Bias Tool	Overall Risk of Bias
(Campochiaro et al., 2010a)	
(Heier et al., 2012)	
(Heier et al., 2014)	
(Hykin et al., 2019)	
(McAllister et al., 2018)	
(Scott et al., 2011)	
(Sen et al., 2021)	
(Sophie et al., 2019)	
(Tadayoni et al., 2017)	
Cohort Studies - CASP Tool	
(Blin et al., 2018)	
(Brown et al., 2014)	
(Calugaru and Calugaru, 2015)	
(Campochiaro et al., 2014)	
(Hikichi et al., 2014)	
(Horner et al., 2020)	
(Inagaki et al., 2019)	
(Khurana et al., 2019)	
(Korobelnik et al., 2016)	
(Larsen et al., 2018)	
(Lee, Jung and Sohn, 2014)	
(Loukianou et al., 2016)	
(Maggio et al., 2020)	
(Mansour et al., 2018)	
(Risard et al., 2011)	
(Sakanishi et al., 2021)	
(Stredova et al., 2019)	
(Volkmann et al., 2020)	
(Wu et al., 2009)	
Case Series - JBI Tool	
(Abdallah et al., 2019)	
(Bajric and Bakri, 2016)	
(Blanc et al., 2018)	
(Busch et al., 2019)	
(Chatziralli et al., 2018)	
(Chatziralli et al., 2017)	
(Chittajallu and Prakash, 2018)	
(Costa et al., 2021)	
(Farinha et al., 2015)	
(Gale et al., 2020)	
(Guichard et al., 2018)	
(Hosogi et al., 2019)	
(Iftikhar et al., 2019)	
(Iida-Miwa et al., 2019)	
(Lo et al., 2020)	
(Lo et al., 2021)	
(Ozkaya, Tarakcioglu and Tanir, 2018)	
(Sophie et al., 2013)	
(Spooner et al., 2019)	
(Tsagkataki et al., 2015)	

Key: Green = low risk of bias. Orange = moderate risk of bias. Red = high risk of bias.

Comparing RVO Types

In CRVO patients, the mean baseline BCVA was 48.2 (95% CI: 44.0-52.4) ETDRS letters and 55.4 (95% CI: 51.7-59.1) letters in BRVO patients; this difference between RVO types at baseline was not significant (p=0.646). After two years BCVA improved in both CRVO and BRVO patients by 9.1 and 10.9 letters respectively; the difference in mean BCVA at two years between CRVO and BRVO patients was not significant (p=0.434). When comparing CRVO, BRVO and mixed RVO patients at baseline and two years, the mixed RVO group achieved an increase of 11.2 letters from 49.7 (95% CI: 42.4-57.1) letters at baseline. The difference between the three RVO groups at baseline was significant (p=0.03) and the difference between the three groups at two years was also significant (p=0.035).

After three years BCVA declined to 53.7 (95% CI: 48.4-59.1) letters in CRVO patients and improved to 67.3 (95% CI: 61.4-73.1) letters in BRVO patients; this difference between RVO types at three years was significant (p=0.003). For CRVO and BRVO patients, BCVA improved up to five years post initial treatment to 63.8 (95% CI: 53.3-74.2) letters and 71.7 (95% CI: 59.0-84.3) letters respectively; however, the differences between baseline and five years for CRVO and BRVO patients were not significant (p=0.172, 0.205) (Figure 2 and Table 6).

Patients with CRVO achieved a greater decrease in CRT over five years follow up, with a mean decrease of 254.2µm compared to 147.8µm decrease in BRVO patients. No data was available for mixed RVO type group beyond three years. However, mean baseline CRT was considerably larger for patients with CRVO, 603.1µm (95% CI: 560.4-645.8) compared to 496.7µm (95% CI: 464.6-528.8). This difference from baseline was not significant in BRVO patients (p=0.058) but was significant in CRVO patients (p=0.012). The overall trend in CRT for each RVO type is summarised in Figure 3. Table 7 provides study and participant numbers with CRT data. For all patients, regardless of RVO type, mean CRT decreased from 554.3µm (95% CI: 527.1-581.6) to 314.4µm (95% CI: 299.2-329.7) after two years, suggesting that intravitreal therapy improves anatomical outcomes in patients with MO due to RVO; this was significant (p<0.01).

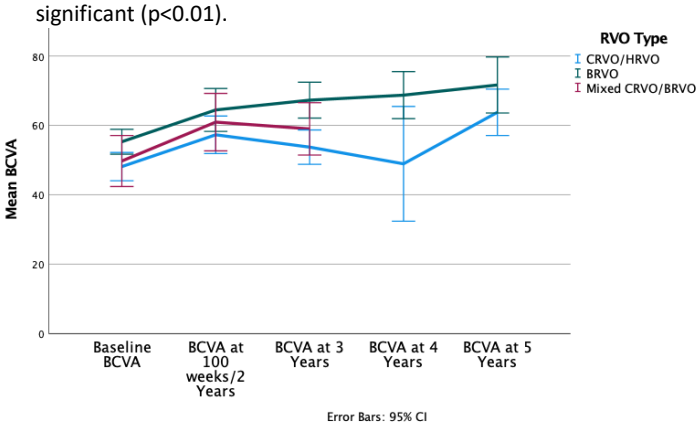

Figure 2. Line Graph of mean BCVA at each timepoint according to RVO type.

TABLE 6. Number of participants and studies with data for BCVA at each timepoint

	No. Studies	No. Participants
Baseline BCVA:	78	10775
BCVA at 2 years:	65	10304
BCVA at 3 years:	25	5775
BCVA at 4 years:	11	501
BCVA at 5 years:	8	402

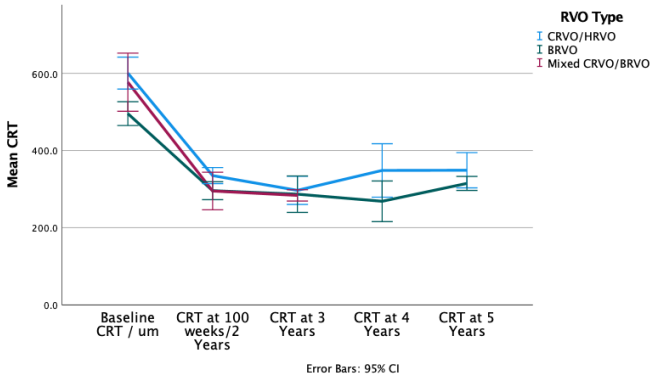

Figure 3. Mean CRT from baseline to five years after initial treatment for each RVO type.

TABLE 7. Number of participants and studies with data for CRT at each timepoint

	No. Studies	No. Participants
Baseline CRT:	69	5486
CRT at 2 years:	57	4887
CRT at 3 years:	21	912
CRT at 4 years:	11	501
CRT at 5 years:	6	381

Comparing Treatments

When treatments were compared mean baseline BCVA was lowest in patients who received combination treatment during the study (49.1 ETDRS letters), however this improved to 56.9 (95% CI: 51.7-62.2) letters and 69.7 (95% CI: 61.2-78.2) letters after two and five years respectively. Not all treatment types had follow-up periods beyond two years, therefore it was difficult to accurately compare outcomes. Twenty-six studies containing 2150 patients who received 'ranibizumab only' had data at two years and showed an improvement in mean BCVA of 8.4 letters from 53.4 (95% CI: 49.1-57.6) letters at baseline to 66.1 (95% CI: 59.9-72.4) at two years; this increase was significant (p= 0.006). Despite this, mean BCVA decreased to 61.8 (95% CI: 19.2-104.3) ETDRS letters in the two studies with data at five years after initial ranibizumab treatment; this difference at five years was not significant when compared to baseline (p=0.077). Patients treated with 'ranibizumab only' had better visual outcomes compared with patients treated with 'dexamethasone only'. For example, at three years mean BCVA in patients treated with 'dexamethasone only' increased by 6.3 letters from 50.1 (95% CI: 41.6-58.6) letters at baseline, however this was not a significant difference at three years (p=0.196). In comparison, patients given 'ranibizumab only' achieved an improvement in mean BCVA of 11.2 letters at three years; this was significant (p=0.001). Figure 4 summarises BCVA data according to treatment type.

Although different treatments had different follow up times, the largest decrease in CRT occurred in patients who received 'bevacizumab only' three years after initial treatment. A decrease of 339.4µm was observed, although the significance could not be calculated due to the small number of studies. The overall trend for CRT at each time point is summarised in Figure 5, according to each treatment type. Patients who received 'ranibizumab only' achieved a decrease in mean CRT of 273.8µm (p=0.451) compared to 'dexamethasone only' patients who achieved a decrease of 209.9µm at three years, from baseline (p=0.02). Patients who received a combination treatment achieved a decrease in mean CRT from 563.2µm (95% CI: 527.9-598.5) at baseline to 331.9µm (95% CI: 297.8-365.9) after five years of treatment, which was significant (p=0.003). Despite this, mean CRT increased between year three and year four by 58.9µm although this was not significant (p=0.961).

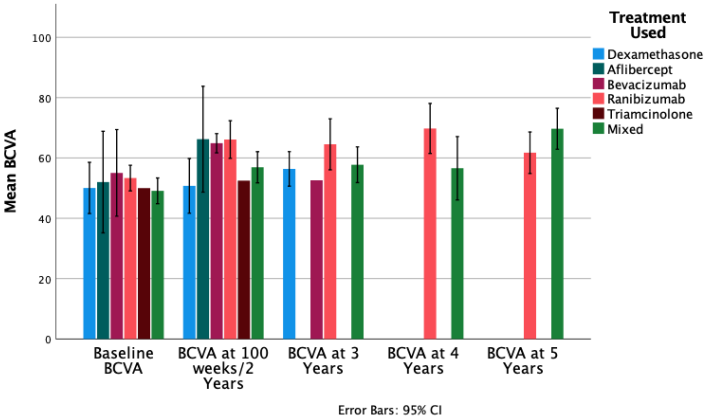

Figure 4. Mean BCVA at each timepoint according to treatment type.

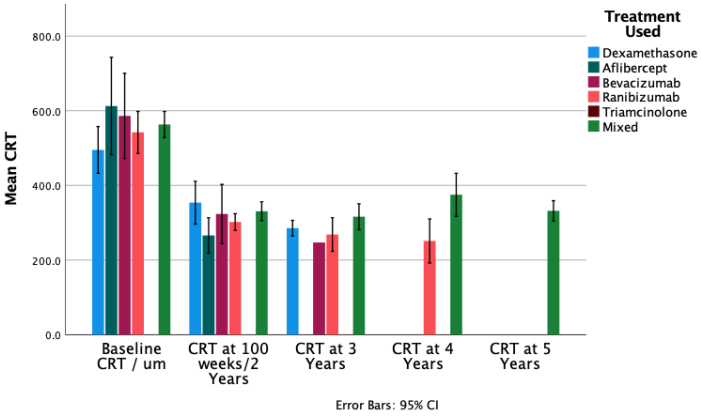

Figure 5. Mean CRT from baseline to five years after initial treatment for each treatment type.

Comparing Study Types

When comparing study types, studies were categorised into two groups, RCTs and non-RCTs, to allow comparison. Included RCTs recorded an improvement in BCVA of 13.6 letters from 55.5 letters at baseline to 69.1 letters at four years (p=0.113) compared to a 10-letter improvement from 50.6 letters at baseline to 60.6 at four years in the non-RCT studies (p=0.002). The difference between RCT and non-RCT at four years was not significant (p=0.501). Figure 6 summarises BCVA data for RCTs and non-RCTs. The largest improvement in mean BCVA from baseline occurred in RCTs, an increase of 14.7 letters, three years after initial treatment; however, this difference was not significant (p=0.054).

The CRT results also varied between RCT and non-RCT studies. Non-RCTs noted a decrease in CRT of 196.8µm from 549.6µm baseline to 352.8µm at four years (p=0.003), whereas RCTs noted a decrease of 366µm from 570.7µm baseline to 204.7µm at four years (p=0.026). The difference between RCT and non-RCT CRT results at four years was not significant (p=0.12). These results reflect a potential benefit in using intravitreal anti-VEGF or steroid therapy long term, beyond two years and are summarised in Figure 7.

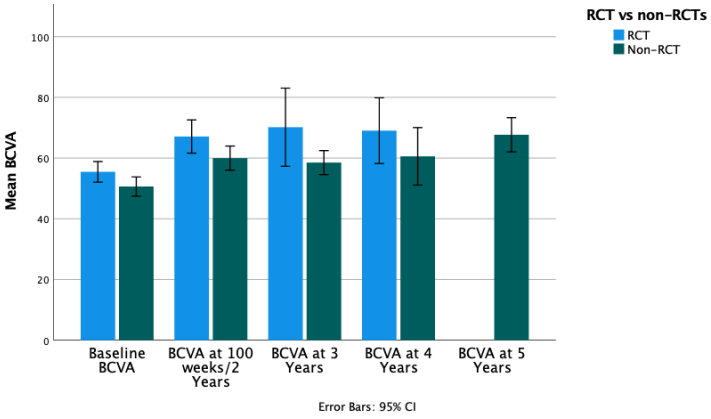

Figure 6. Bar Graph comparing mean BCVA in RCT against non-RCT studies at each timepoint.

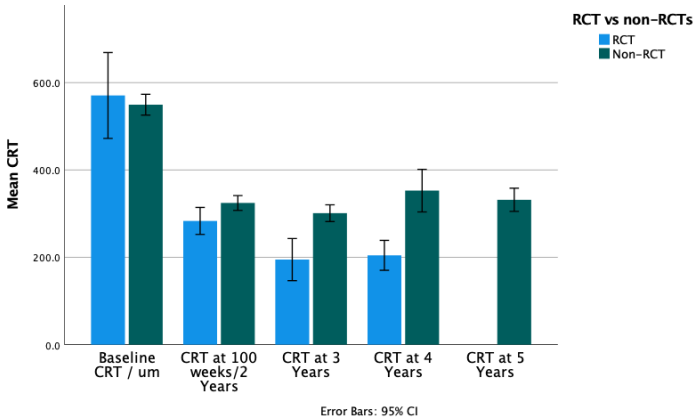

Figure 7. Bar Graph comparing mean CRT in RCT against non-RCT studies at each timepoint.

DISCUSSION

This systematic review revealed sustained benefit and a modest improvement in the long-term outcomes for patients treated with intravitreal anti-VEGF or steroid injections for macular oedema secondary to retinal vein occlusion. Mean BCVA improved from baseline up to five years, by 16.1 ETDRS letters overall.

The inclusion criteria were set to investigate the full range of real-world evidence available by including various study designs. Although they are the gold standard, RCT studies represent the ideal scenario with guaranteed scheduled visits and higher patient compliance, which therefore may provide potentially better results than real-world studies (Ziemssen et al., 2017). For example, in the ANCHOR RCT, which analysed age-related macular degeneration (AMD) patients over two years with ranibizumab treatment against photodynamic therapy, mean BCVA improved by 11.3 letters in the ranibizumab group from baseline to year one (Brown et al., 2006). In comparison, the real-world LUMINOUS study noted a gain of 3.1 letters over 12 months in patients treated with ranibizumab (Koh et al., 2020). This example highlights the potential differences in results between RCT and non-RCT studies despite the same treatment being used over the same timeframe.

In our study, when comparing RCT and non-RCT studies, patients enrolled in RCT trials also achieved better functional and anatomical outcomes. Patients in RCTs achieved an increase of 13.6 letters at four years compared to an increase of 10 letters in patients within non-RCT studies, the difference at four years was not significant (p=0.501). Year four results were compared as five-year data was not available for included RCT studies. Analysing anatomical outcomes in RCT studies, patients attained a decrease in CRT of 366µm at four years from 570.7µm baseline, compared to a decrease of 196.8µm at four years in patients enrolled on non-RCT studies, from 549.6µm baseline. This difference at four years was not significant (p=0.12). One possible reason for differences in results include the number and frequency of intravitreal injections between RCTs and non-RCTs, however due to inconsistent reporting of injection frequency this was not analysed in this review. In addition, other potential reasons include the strict eligibility criteria for RCTs and exclusion of patients with poor baseline vision or co-morbidities. However, a non-significant trend was observed in results between RCTs and non-RCTs. This suggests our review was underpowered for this comparison and larger study samples are needed to comprehensively compare results from RCTs and non-RCTs. This presents the challenge to clinicians to balance the efficacy of treatment regimen with patient compliance and treatment burden, particularly if anti-VEGF treatment is used long term.

Therefore, to maximise the available information this systematic review included RCT, cohort, prospective case series and retrospective case series, and grouped results into RCTs and non-RCTs accordingly.

When the final recorded BCVA in CRVO and BRVO patients was compared, no significant difference was found at five years (p= 0.178). Patients with BRVO improved from 55.4 letters (95% CI: 51.7-59.1) to 71.7 (95% CI: 59.0-84.3) letters and CRVO patients improved from 48.2 (95% CI: 44.0-52.4) letters to 63.8 (95% CI: 53.3-74.2) letters at year five. The lower BCVA values in CRVO patients occurs because a CRVO affects a larger area of the retina, further reducing vision. Patients with CRVO achieved a decrease in mean CRT of 254.2µm from 603.1µm (95% CI: 560.4-645.8) at baseline compared to a decrease of 181.9µm from 496.7µm (95% CI: 464.6-528.8) at baseline in BRVO patients. The differences between CRT at five years were also not significant (p=0.232). The larger decrease in CRVO patients may be explained by the larger baseline value, meaning there was more potential to reduce oedema.

When comparing long term outcomes for different treatment types, results varied slightly. The study numbers for individual drugs were too small to draw any significant conclusions after three years. Twenty-eight studies comprising 2262 patients investigated use of ranibizumab only. At two years, mean BCVA improved by 12.7 letters from 53.4 (95% CI: 59.9-72.4) letters at baseline, this improvement at two years was significant (p<0.01). Studies investigating dexamethasone recorded an improvement in mean BCVA from baseline 50.1 (95% CI: 41.6-58.6) letters to three years of 6.3 ETDRS letters. However, the small study numbers may have skewed results and further investigation is needed to draw a solid conclusion. Another consideration with repeated steroid injections is the risk of developing cataracts (Gillies et al., 2004). This may account for some of the poorer responses noted with dexamethasone in this review. The analysis of cataract incidence was beyond the scope of this study; however, it could be analysed in follow-up studies. Anatomical outcomes also varied for different treatments as discussed previously. In patients treated with a combination treatment, mean CRT increased between years three and four by 58.8µm. Due to the large number of combination therapies in included studies, if more than one therapy was given to a patient this was grouped into the 'combination treatment' category, therefore making direct comparisons difficult. The necessity to switch patients from one drug to another would usually result from lack of efficacy in the original drug in certain patients, which required a 'trial and error' process until the patient responded adequately to a treatment. Patients who received ranibizumab only achieved consistent reduction in mean CRT from 542.2µm (95% CI: 485.6-598.7) baseline to 251.1µm (95% CI: 159.7-342.4) after four years, which was significant (p=0.003).

Best corrected visual acuity and CRT follow similar trends in improvement due to the inherent link between retinal anatomy and visual function. When CRT is high, this indicates that the retinal structure is disrupted by MO, therefore damaging intercellular relationships within the retina, disturbing the visual signals and subsequently affecting BCVA. Macular oedema itself may also be toxic to the retina, reducing patient's vision (Bakri et al., 2016). However, some limiting factors to the association between CRT reduction and BCVA improvement include the existence of non-central macular oedema, meaning CRT measurement may not always capture the full extent or effect of oedema in the retina. Also, if CRT was particularly low other factors must be considered such as retinal atrophy, particularly in diseases such as AMD therefore CRT alone cannot be reliably used as an accurate predictor or measure of visual function (Bell et al., 2017).

Intravitreal anti-VEGF injections have been proven effective and are used first line in treating MO secondary to other diseases including diabetic macular oedema (DMO) and AMD (Downey et al., 2021; Scott and Bressler, 2013). In the VISION study, long term outcomes for patients with DMO treated with ranibizumab were investigated (Van Aken et al., 2020). An improvement in BCVA was reported from 59 ETDRS letters baseline to 67.9 and 64.8 letters at two and three years respectively. In comparison to our study, overall mean baseline BCVA was 7.4 letters less (51.6) in our sample; despite this, patients achieved similar vision gain over two years, 9.2 letters compared to 8.9 letters in the VISION study. The difference in baseline BCVA between our sample and the VISION study patients may be accounted for by the sudden nature of an RVO insult compared to the typically gradual onset of MO in DMO patients. When analysing anatomical outcomes, CRT improved by 111µm in the VISION study from 429µm baseline to 318µm and 381µm at two and three years respectively. In comparison, our sample of patients treated only with ranibizumab achieved a 240.3µm decrease in CRT from 542.2µm baseline to 301.9 and 268.4µm at two and three years respectively.

The Protocol T Extension study (Glassman et al., 2020) was an RCT investigating long term outcomes of patients with MO secondary to DMO treated with either aflibercept, bevacizumab or ranibizumab over five years. It noted an overall improvement in BCVA of 12.1 letters from 65.7 ETDRS letters at baseline to 77.8 letters at year two. This compares with our review results as mentioned previously. The difference in baseline and subsequent improvement in BCVA may be accounted for by the differences in study design between RCT and our review, encompassing various study designs. When comparing

DMO and RVO patients treated with aflibercept, results were similar between studies over two years. In the Protocol T study, patients improved by 12.4 letters from 66.3 letters baseline compared to an improvement of 14.2 letters from 52 letters at baseline in our review. However, our small sample size limits conclusions. In the Protocol T Extension study, CRT values also improved over the five years, decreasing by 154µm overall compared to a reduction of 222.5µm in our study (554.2µm baseline). The further decrease in our review may be due to the retinal health of RVO patients compared to diabetic patients. This study had a large sample size (n=317) increasing validity of their results as well as random assignment to different anti-VEGF therapies. However, 32% of participants were lost to follow-up, this group had worse baseline BCVA, therefore skewing long-term results.

In the VIEW study, patients with AMD were treated with ranibizumab and aflibercept combination and 96-week outcomes were analysed (Schmidt-Erfurth et al., 2014). Mean BCVA improved between 6.6-7.9 letters from 52.8 and 54 letters at baseline in the aflibercept and ranibizumab groups. Subsequently, aflibercept was found non-inferior to ranibizumab. In this study, AMD patients achieved less positive visual outcomes when compared with RVO patients in our study, despite similar baseline BCVA values. The randomised, double masked nature of this study increases validity of results as does the large sample size of 2457 participants with AMD. The difference in BCVA improvement between AMD and RVO patients may be explained by the typical patient demographic with these conditions. Age-related macular degeneration is a chronic, degenerative and progressive condition, usually seen in older patients, compared to RVO which is typically a single acute event in patients with risk factors such as hypertension, hyperlipidaemia or diabetes (RCOphth, 2015).

The strengths of this study included, firstly, the comprehensiveness of the search strategy to ensure the relevant studies were not missed (3050 studies were screened across the four databases); and secondly, the broad inclusion criteria to reflect the range of real-world practice. Two variables were analysed, BCVA and CRT, and compared across different categories including RVO type, treatment type and study type to increase real-world generalisability. Although no formal analysis was performed on the interaction of these different categories, the likelihood of them confounding results in clinical practice is low. Without formal analysis, however, the risk of confounding results is present, although we believe this to be small.

The heterogeneity of study designs prevented a formal meta-analysis to determine definitive BCVA and CRT outcomes, although this had been an intention of our approach to increase real-world generalisability. Another limitation was the lack of long-term data for all comparators, for example only patients treated with ranibizumab and combination treatment had BCVA data up to five years, the rest only had to three years. This made direct comparisons difficult beyond three years for BCVA.

The heterogeneity led to varied study characteristics. Thirty-three studies followed patients for up to two years (Busch et al., 2019) whereas others had up to five years follow up (Spooner et al., 2019). Studies varied according to the data source used, for example most retrospective studies reviewed electronic medical records (Bajric and Bakri, 2016), whereas RCT and prospective cohort studies recorded data after each visit (Sen et al., 2021). Twenty-eight studies excluded patients with MO due to other pathology (Ozkaya, Tarakcioglu and Tanir, 2018). Twenty-six studies included only treatment naïve patients. Whereas in six studies, although baseline BCVA prior to original treatment was not recorded, patients with previous treatment for MO due to RVO were not excluded (Mansour et al., 2018) and in the other 16 it was not stated explicitly. Some studies set a baseline BCVA and CRT measurement for inclusion (Heier et al., 2014; Mansour et al., 2018). Ten studies included separate data for both CRVOs and BRVOs (Hykin et al., 2019) and ten included CRVO data only (Calugaru and Calugaru, 2015), while 12 included BRVO data only (Hikichi et al., 2014). The remaining six studies either combined data or did not specify RVO type and therefore it was assumed to contain both CRVO and BRVO patients (Volkmann et al., 2020). Studies varied on use of equipment to measure CRT. Nineteen studies used the Heidelberg Spectralis OCT machine (Spooner et al., 2019). Thirteen studies used the Cirrus HD-OCT, Carl Zeiss Meditec OCT machine (Wu et al., 2009) and two used the 3D-OCT 2000 OCT machine (Horner et al., 2020; Maggio et al., 2020). The other studies did not specify what equipment was used. One RCT randomised patients to receive a certain drug against sham (McAllister et al., 2018); the outcomes for patients in the sham arm were disregarded. Three RCTs randomised patients to receive different doses of the same drug (Tadayoni et al., 2017), which were recorded as one data input and three randomised patients into different treatment groups and results were recorded separately for the purposes of our study (Hykin et al., 2019).

Going forward, further studies should be undertaken to investigate long term outcomes of intravitreal anti-VEGF injections for MO secondary to RVO to strengthen the existing evidence of positive outcomes. An obstacle faced in this systematic review was the various primary outcomes and methods used to measure BCVA and CRT results, for example, some recorded percentage of patients who improved BCVA by 15 letters while others recorded change in values or graphical

trends only. Much potentially useful data was lost due to our exclusion of 27 studies which included data which was either unclear, in the form of graphs or where only changes in BCVA or CRT, rather than absolute values, were provided. Therefore, further RCTs with consistent output variables should be undertaken. Ideally these RCTs would have consistent measurements of BCVA and CRT and consistent primary outcomes to allow direct comparisons between studies.

As anti-VEGFs are used more extensively, long-term prospective studies are needed to investigate patient outcomes beyond the first few years of treatment. It is important to remember the impact these disorders and treatments have on patients and to accurately assess this impact in large scale QOL studies to better inform patients and clinicians. Data in this field was lacking in our sample, with only one study recording QOL data (Korobelnik et al., 2016); therefore, studies investigating QOL in patients taking intravitreal injections for MO due to RVO are essential. In addition, more studies investigating the long-term cost-effectiveness of intravitreal anti-VEGF or steroid therapy, balanced with the long-term benefits to patients should be conducted.

Overall, this systematic review provides both real world and RCT evidence of long-term benefits for patients with MO due to both CRVO and BRVO, treated with anti-VEGF or steroid injections.

CONCLUSIONS

The results of this study support the conclusion that intravitreal anti-VEGF or steroid therapy for MO due to RVO is beneficial long-term up to five years after initial treatment and suggests patients can at least maintain BCVA improvement from the initial treatment and may even further improve BCVA with increased long-term treatment. Anatomical outcomes for patients on long-term anti-VEGF or steroid therapy are also positive, with an overall reduction in CRT observed from baseline to five years, across the different interventions. This review has provided an answer to patients' real-world questions about the long-term outcomes of intravitreal anti-VEGF or steroid treatment for MO due to RVO, and what to expect both from participation in an RCT and in the 'real-world' setting.

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REFERENCES

Abdallah, W., Barakat, M., Goldenberg, D., Itty, S., Dugel, P. U., Jamal, K., Kunimoto, D., Mehta, S., Quinlan, E. & Palejwala, N. 2019. Assessing the efficacy and safety of intravitreal dexamethazone implant in treating macular edema in eyes with an incomplete response to anti-vascular endothelial growth factor agents. *Investigative Ophthalmology and Visual Science. Conference,* 60.

Bajric, J. & Bakri, S. J. 2016. Outcomes of patients initially treated with intravitreal bevacizumab for central retinal vein occlusion: Long-term follow-up. *Seminars in Ophthalmology,* 31**,** 542-547.

Bakri, S. J., Berrocal, A., Capone, A., Choudhry, N., Ciulla, T., Dugel, P. U., Emerson, G. G., Freund, K. B., Goldberg, R. A. & Et Al. 2016. *Macular oedema* [Online]. American Society of Retina Specialists. Available: https://www.asrs.org/patients/retinal-diseases/20/macular-edema [Accessed].

Bell, K. J., Hayen, A., Glasziou, P., Mitchell, A. S., Farris, M., Wright, J., Duerr, H. P., Mitchell, P. & Irwig, L. 2017. Early crt monitoring using time-domain optical coherence tomography does not add to visual acuity for predicting visual loss in patients with central retinal vein occlusion treated with intravitreal ranibizumab: A secondary analysis of trial data. *Retina,* 37**,** 509-514.

Blanc, J., Deschasse, C., Kodjikian, L., Dot, C., Bron, A. M. & Creuzot-Garcher, C. 2018. Safety and long-term efficacy of repeated dexamethasone intravitreal implants for the treatment of cystoid macular edema secondary to retinal vein occlusion with or without a switch to anti-vegf agents: A 3-year experience. *Graefes Archive for Clinical & Experimental Ophthalmology,* 256**,** 1441-1448.

Blin, P., Delcourt, C., Glacet-Bernard, A., Creuzot-Garcher, C., Fajnkuchen, F., Girmens, J. F., Guillausseau, P. J., Kodjikian, L., Massin, P., Mahe, M., Lassalle, R., Bernard, M. A., Chartier, A., Maizi, H., Droz-Perroteau, C., Grolleau, A., Grelaud, A. & Moore, N. 2018. Effectiveness of ranibizumab intravitreal injections in visual impairment due to macular edema secondary to retinal vein occlusion: Final results at 24 months from the french boreal cohort. *Pharmacoepidemiology and Drug Safety,* 27 (Supplement 2)**,** 409-410.

Brown, D., Kaiser, P. K., Michels, M., Soubrane, G., Heier, M. D., Kim, R., Judy, P. & Schneider, S. 2006. Ranibizumab versus verteporfin for

neovascular age-related macular degeneration. *The New England Journal of Medicine,* 355**,** 1432-44.

Brown, D. M., Wykoff, C. C., Wong, T. P., Mariani, A. F., Croft, D. E., Schuetzle, K. L. & Grp, R. S. 2014. Ranibizumab in preproliferative (ischemic) central retinal vein occlusion the rubeosis anti-vegf (rave) trial. *Retina-the Journal of Retinal and Vitreous Diseases,* 34**,** 1728-1735.

Brown, G. 1999. Vision and quality-of-life. *Transactions of the American Ophthalmological Society,* 97**,** 473-511.

Busch, C., Rehak, M., Sarvariya, C., Zur, D., Iglicki, M., Lima, L. H., Invernizzi, A., Viola, F., Agrawal, K., Sinawat, S., Couturier, A., Mehta, A., Juneja, R., Jain, H., Agarwal, A. K., Goel, N., Nagpal, M., Gupta, V., Banker, A., Loewenstein, A., Okada, M., Saatci, A. O., Mansour, A. M. & Chhablani, J. 2019. Long-term visual outcome and its predictors in macular oedema secondary to retinal vein occlusion treated with dexamethasone implant. *British Journal of Ophthalmology,* 103**,** 463-468.

Calugaru, D. & Calugaru, M. 2015. Intravitreal bevacizumab in acute central/hemicentral retinal vein occlusions: Three-year results of a prospective clinical study. *Journal of Ocular Pharmacology and Therapeutics,* 31**,** 78-86.

Campochiaro, P. A., Clark, W. L., Boyer, D. S., Heier, J. S., Brown, D. M., Vitti, R. & Et Al. 2015. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: The 24-week results of the vibrant study. *Ophthalmology,* 122**,** 538-544.

Campochiaro, P. A., Hafiz, G., Channa, R., Shah, S. M., Nguyen, Q. D., Ying, H., Do, D. V., Zimmer-Galler, I., Solomon, S. D., Sung, J. U. & Syed, B. 2010a. Antagonism of vascular endothelial growth factor for macular edema caused by retinal vein occlusions: Two-year outcomes. *Ophthalmology,* 117**,** 2387-2394.e1-5.

Campochiaro, P. A., Heier, J. S., Feiner, L., Rubio, R. G., Abraham, P., Alfaro, D. V., Awh, C. C., Baker, C., Bakri, S. J., Barile, G. R., Bennett, M., Berger, B. B. & Et Al. 2010b. Ranibizumab for macular edema following branch retinal vein occlusion: Six-month primary end point results of a phase iii study. . *Ophthalmology,* 117**,** 1102-1112.

Campochiaro, P. A., Sophie, R., Pearlman, J., Brown, D. M., Boyer, D. S., Heier, J. S., Marcus, D. M., Feiner, L., Patel, A. & Group, R. S. 2014. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: The retain study. *Ophthalmology,* 121**,** 209-219.

Casp 2018. Critical appraisal skills programme cohort study checklist. online.

Chatziralli, I., Theodossiadis, G., Chatzirallis, A., Parikakis, E., Mitropoulos, P. & Theodossiadis, P. 2018. Ranibizumab for retinal vein occlusion: Predictive factors and long-term outcomes in real-life data. *Retina,* 38**,** 559-568.

Chatziralli, I., Theodossiadis, G., Parikakis, E., Mitropoulos, P. G. & Theodossiadis, P. 2017. Long-term anatomical and functional outcomes in patients with ischemic central retinal vein occlusion treated with anti-vascular endothelial growth factor agents. *Ophthalmic Research,* 58**,** 203-208.

Chittajallu, N. & Prakash, P. 2018. Intravitreal ranibizumab for the treatment of macular oedema associated with branch retinal vein occlusion (brvo): Results for 3 years. *Eye (Basingstoke),* 32 (11)**,** 10-11.

Costa, J. V., Moura-Coelho, N., Abreu, A. C., Neves, P., Ornelas, M. & Furtado, M. J. 2021. Macular edema secondary to retinal vein occlusion in a real-life setting: A multicenter, nationwide, 3-year follow-up study. *Graefe's Archive for Clinical and Experimental Ophthalmology,* 259**,** 343-350.

Downey, L., Acharya, N., Devonport, H., Gale, R., Habib, M., Manjunath, V., Mukherjee, R. & Severn, P. 2021. Treatment choices for diabetic macular oedema: A guideline for when to consider an intravitreal corticosteroid, including adaptations for the covid-19 era. *BMJ Open Ophthalmol,* 6**,** e000696.

Farinha, C., Marques, J. P., Almeida, E., Baltar, A., Santos, A. R., Melo, P., Costa, M., Figueira, J., Cachulo, M. L., Pires, I. & Silva, R. 2015. Treatment of retinal vein occlusion with ranibizumab in clinical practice: Longer-term results and predictive factors of functional outcome. *Ophthalmic Research,* 55**,** 10-8.

Gale, R., Gill, C., Pikoula, M., Lee, A. Y., Hanson, R. L. W., Denaxas, S., Egan, C., Tufail, A. & Taylor, P. 2020. Multicentre study of 4626 patients assesses the effectiveness, safety and burden of two categories of treatments for central retinal vein occlusion: Intravitreal anti-vascular endothelial growth factor injections and intravitreal ozurdex injections. *The British journal of ophthalmology.,* 22.

Gillies, M., Simpson, J. M., Billson, F. A., Luo, W. J., P., P., Chua, W., Mirtchell, P., Zhu, M. D. & Hunyor, A. 2004. Safety of an intravitreal injection of triamcinolone: Results from a randomized

clinical trial. *Arch Ophthalmology,* 122**,** 336-340.

Glassman, A. R., Wells, J. A., 3rd, Josic, K., Maguire, M. G., Antoszyk, A. N., Baker, C., Beaulieu, W. T., Elman, M. J., Jampol, L. M. & Sun, J. K. 2020. Five-year outcomes after initial aflibercept, bevacizumab, or ranibizumab treatment for diabetic macular edema (protocol t extension study). *Ophthalmology,* 127**,** 1201-1210.

Guichard, M. M., Xavier, A. R., Turksever, C., Pruente, C. & Hatz, K. 2018. Spectral-domain optical coherence tomography-driven treat-and-extend and pro re nata regimen in patients with macular oedema due to retinal vein occlusion: 24-month evaluation and outcome predictors. *Ophthalmic Research,* 60**,** 29-37.

Haller, J. A., Bandello, F., Belfort, R., Blumenkranz, M., Gillies, M., Heier, J., Loewenstein, A., Yoon, Y. H., Jacques, M. L., Jiao, J., Li, X. Y., Whitcup, S. M. & Group, O. G. S. 2010. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology,* 117**,** 1134-1146.

Heier, J. S., Campochiaro, P. A., Yau, L., Li, Z., Saroj, N., Rubio, R. G. & Lai, P. 2012. Ranibizumab for macular edema due to retinal vein occlusions: Long-term follow-up in the horizon trial. *Ophthalmology,* 119**,** 802-809.

Heier, J. S., Clark, W. L., Boyer, D. S., Brown, D. M., Vitti, R., Berliner, A. J., Kazmi, H., Ma, Y., Stemper, B., Zeitz, O. & Et Al. 2014. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: Two-year results from the copernicus study. *Ophthalmology,* 121**,** 1414-1420.e1.

Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, K. F., Weeks, L., Sterne, J. A., Cochrane Bias Methods, G. & Cochrane Statistical Methods, G. 2011. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ,* 343**,** d5928.

Hikichi, T., Higuchi, M., Matsushita, T., Kosaka, S., Matsushita, R., Takami, K., Ohtsuka, H., Kitamei, H. & Shioya, S. 2014. Two-year outcomes of intravitreal bevacizumab therapy for macular oedema secondary to branch retinal vein occlusion. *British Journal of Ophthalmology,* 98**,** 195-199.

Horner, F., Lip, P. L., Mushtaq, B., Chavan, R., Mohammed, B. & Mitra, A. 2020. Combination therapy for macular oedema in retinal vein occlusions: 3-year results from a real-world clinical practice. *Clinical Ophthalmology,* 14**,** 955-965.

Hosogi, M., Shiode, Y., Morizane, Y., Kimura, S., Hosokawa, M., Doi, S., Toshima, S., Takahashi, K., Fujiwara, A. & Shiraga, F. 2019. Two-year results of intravitreal ranibizumab injections using a treat-and-extend regimen for macular edema due to branch retinal vein occlusion. *Acta Medica Okayama,* 73**,** 517-522.

Hykin, P., Prevost, A. T., Vasconcelos, J. C., Murphy, C., Kelly, J., Ramu, J., Hounsome, B., Yang, Y., Harding, S. P., Lotery, A., Chakravarthy, U., Sivaprasad, S., Eleftheriadis, H., Briggs, M., Williams, M., Abugreen, S., Ghanchi, F., Narendran, N., Hughes, E., Ross, A., Gupta, N., Turner, S., Osoba, Y., Patel, J., Pagliarini, S., Lip, P. L., Patel, N., Jafree, A., Menon, G., Patra, S., Burton, B., Taylor, S., Mackenzie, S., Gale, R., Vadivelu, K., Mckibbin, M., George, S., Almeida, G., Sen, P., Patrao, N., Menon, D., Nicholson, L., D'souza, Y., Talks, J., Sundaram, V., Banerjee, S., Habib, M., Ram, R., Brand, C., Newman, D., Gilmour, D., Kelly, S., Khan, R., Empeslidis, T., Jones, C., Fletcher, E., Downey, L., Younis, S., Severn, P., Prakash, P., Lever, E., Downes, S., Stratton, I., Dodhia, H., Fell, G., Asaria, R., Byrne, J., Burgess, V., Powling, A., Ryde, M., Walker, S., Moorman, C., Dhillon, B. & Grp, L. S. 2019. Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion a randomized clinical trial. *Jama Ophthalmology,* 137**,** 1256-1264.

Iftikhar, M., Mir, T. A., Hafiz, G., Zimmer-Galler, I., Scott, A. W., Solomon, S. D., Sodhi, A., Wenick, A. S., Meyerle, C., Jiramongkolchai, K., Liu, T. Y. A., Arevalo, J. F., Singh, M., Kherani, S., Handa, J. T. & Campochiaro, P. A. 2019. Loss of peak vision in retinal vein occlusion patients treated for macular edema. *American Journal of Ophthalmology,* 205**,** 17-26.

Iida-Miwa, Y., Muraoka, Y., Iida, Y., Ooto, S., Murakami, T., Suzuma, K. & Tsujikawa, A. 2019. Branch retinal vein occlusion: Treatment outcomes according to the retinal nonperfusion area, clinical subtype, and crossing pattern. *Scientific Reports,* 9.

Inagaki, M., Hirano, Y., Suzuki, N., Yasuda, Y., Kawamura, M., Yasukawa, T., Yoshida, M. & Ogura, Y. 2019. Twenty-four month results of intravitreal ranibizumab for macular edema after branch retinal vein occlusion in a single-center prospective study: Visual prognosis and rate of complete resolution of macular edema. *Investigative Ophthalmology & Visual Science,* 60.

Khurana, R. N., Chang, L. K., Bansal, A. S., Palmer, J. D., Wu, C. & Wieland, M. R. 2019. Treat and extend regimen with aflibercept for chronic central retinal vein occlusions: 2 year results of the newton study. *International Journal of Retina and Vitreous,* 5**,** 1-7.

Koh, A., Lai, T. Y., Wei, W., Mori, R., Wakiyama, H., Park, K. H., Ngah, F., Macfadden, W., Dunger-Baldauf, C. & Parikh, S. 2020. Real-world effectiveness and safety of ranibizumab treatment in patients with and without polypoidal choroidal vasculopathy
twelve-month results from the luminous study. *Retina,* 40**,** 1529-1539.

Korobelnik, J. F., Kodjikian, L., Delcourt, C., Gualino, V., Leaback, R., Pinchinat, S. & Velard, M. E. 2016. Two-year, prospective, multicenter study of the use of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in the clinical setting in france. *Graefes Archive for Clinical & Experimental Ophthalmology,* 254**,** 2307-2318.

Larsen, M., Waldstein, S. M., Priglinger, S., Hykin, P., Barnes, E., Gekkieva, M., Das Gupta, A., Wenzel, A., Mones, J. & Group, C. S. 2018. Sustained benefits from ranibizumab for central retinal vein occlusion with macular edema: 24-month results of the crystal study. *Ophthalmology Retina,* 2**,** 134-142.

Lee, K., Jung, H. & Sohn, J. 2014. Comparison of injection of intravitreal drugs with standard care in macular edema secondary to branch retinal vein occlusion. *Korean Journal of Ophthalmology,* 28**,** 19-25.

Lo, T., Lent-Schochet, D., Luu, K. Y., Kuriyan, A. E., Weiss, M. Y., Rachitskaya, A., Singh, R. P., Wai, K. M., Campbell, J. P., Gupta, K., Nudleman, E., Chen, K. C. & Yiu, G. 2020. Factors associated with visual outcomes and treatment discontinuation in eyes with retinal vein occlusion and macular edema in real-world settings. *Investigative Ophthalmology and Visual Science. Conference,* 61.

Lo, T., Lent-Schochet, D., Luu, K. Y., Kuriyan, A. E., Weiss, M. Y., Rachitskaya, A. V., Singh, R. P., Wai, K. M., Campbell, J. P., Gupta, K., Nudleman, E., Chen, K. C. & Yiu, G. 2021. Patterns and predictors of successful treatment discontinuation in retinal vein occlusions with macular edema in the real world. *Ophthalmic Surgery Lasers & Imaging Retina,* 52**,** 84-92.

Loukianou, E., Brouzas, D., Chatzistefanou, K. & Koutsandrea, C. 2016. Clinical, anatomical, and electrophysiological assessments of the central retina following intravitreal bevacizumab for macular edema secondary to retinal vein occlusion. *International Ophthalmology,* 36**,** 21-36.

Maggio, E., Mete, M., Maraone, G., Attanasio, M., Guerriero, M. & Pertile, G. 2020. Intravitreal injections for macular edema secondary to retinal vein occlusion: Long-term functional and anatomic outcomes. *Journal of Ophthalmology,* 2020.

Mansour, A. M., Ashraf, M., Charbaji, A., Younis, M. H., Souka, A. A., Dogra, A., Mansour, H. A., Chhablani, J. & Ziv-Aflibercept Study Group, i. 2018. Two-year outcomes of intravitreal ziv-aflibercept. *British Journal of Ophthalmology,* 102**,** 1387-1390.

Mcallister, I. L., Smithies, L. A., Chen, F. K., Mackey, D. A. & Sanfilippo, P. G. 2018. Two-year efficacy of ranibizumab plus laser-induced chorioretinal anastomosis vs ranibizumab monotherapy for central retinal vein occlusion: A randomized clinical trial. *JAMA ophthalmology,* 136**,** 1391-1397.

Munn Z, Barker T, Moola S, Tufanaru C, Stern C, Mcarthur A, Stephenson M & E., A. 2020. Methodological quality of case series studies,. *JBI Evidence Synthesis.*

Noma, H., Yasuda, K. & Shimura, M. 2020. Cytokines and pathogenesis of central retinal vein occlusion. *J Clin Med,* 9.

Ozkaya, A., Tarakcioglu, H. N. & Tanir, I. 2018. Ranibizumab versus dexamethasone implant in macular edema secondary to branch retinal vein occlusion: Two-year outcomes. *Optometry and Vision Science,* 95**,** 1149-1154.

Page, M. J., Mckenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hrobjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., Mcdonald, S., Mcguinness, L. A., Stewart, L. A., Thomas, J., Tricco, A. C., Welch, V. A., Whiting, P. & Moher, D. 2021. The prisma 2020 statement: An updated guideline for reporting systematic reviews. *BMJ,* 372**,** n71.

Pielen, A., Clark, W. L., Boyer, D. & Et Al. 2017. Integrated results from the copernicus and galileo studies. *Clinical Ophthalmology,* 11**,** 1533-1540.

Rcophth 2015. Retinal vein occlusion rvo guidelines. *RCO Guidelines.*

Risard, S. M., Pieramici, D. J., Rabena, M. D., Basefsky, J. C., Avery, R. L., Castellarin, A. A., Nasir, M. A., See, R. F. & Couvillion, S. S. 2011. Intravitreal

ranibizumab for macular edema secondary to central retinal vein occlusion. *Retina,* 31**,** 1060-7.

Rubio, R. & Genentech, I. 2011. A study of the efficacy and safety of ranibizumab injection in patients with macular edema secondary to central retinal vein occlusion (cruise). U.S National Library of Medicine.

Sakanishi, Y., Yasuda, K., Morita, S., Mashimo, K., Tamaki, K., Sakuma, T. & Ebihara, N. 2021. Twenty-four-month results of intravitreal aflibercept for macular edema due to branch retinal vein occlusion. *Japanese Journal of Ophthalmology,* 65**,** 63-68.

Schmidt-Erfurth, U., Kaiser, P. K., Korobelnik, J. F., Brown, D. M., Chong, V., Nguyen, Q. D., Ho, A. C., Ogura, Y., Simader, C., Jaffe, G. J., Slakter, J. S., Yancopoulos, G. D., Stahl, N., Vitti, R., Berliner, A. J., Soo, Y., Anderesi, M., Sowade, O., Zeitz, O., Norenberg, C., Sandbrink, R. & Heier, J. S. 2014. Intravitreal aflibercept injection for neovascular age-related macular degeneration: Ninety-six-week results of the view studies. *Ophthalmology,* 121**,** 193-201.

Scott, A. & Bressler, S. 2013. Long-term follow-up of vascular endothelial growth factor inhibitor therapy for neovascular age-related macular degeneration. *Current Opinion Ophthalmology,* 24**,** 190-196.

Scott, I. U., Vanveldhuisen, P. C., Oden, N. L., Ip, M. S., Blodi, B. A., Hartnett, M. E., Cohen, G. & Stand Care Versus, C. 2011. Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard care versus corticosteroid for retinal vein occlusion study report 10. *Ophthalmology,* 118**,** 345-352.

Sen, P., Gurudas, S., Ramu, J., Patrao, N., Chandra, S., Rasheed, R., Nicholson, L., Peto, T., Sivaprasad, S. & Hykin, P. 2021. Predictors of visual acuity outcomes after anti-vascular endothelial growth factor treatment for macular edema secondary to central retinal vein occlusion. *Ophthalmology Retina.*

Song, P., Xu, Y., Zha, M., Zhang, Y. & Rudan, I. 2019. Global epidemiology of retinal vein occlusion: A systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health,* 9**,** 010427.

Sophie, R., Hafiz, G., Scott, A. W., Zimmer-Galler, I., Nguyen, Q. D., Ying, H., Do, D. V., Solomon, S., Sodhi, A., Gehlbach, P. & Et Al. 2013. Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal nonperfusion. *American journal of ophthalmology,* 156**,** 693-705.

Sophie, R., Wang, P. W., Channa, R., Quezada-Ruiz, C., Clark, A. & Campochiaro, P. A. 2019. Different factors associated with 2-year outcomes in patients with branch versus central retinal vein occlusion treated with ranibizumab. *Ophthalmology,* 126**,** 1695-1702.

Spooner, K., Fraser-Bell, S., Hong, T. & Chang, A. A. 2019. Five-year outcomes of retinal vein occlusion treated with vascular endothelial growth factor inhibitors. *Bmj Open Ophthalmology,* 4.

Sterne, J. A. C., Savovic, J., Page, M., Elbers, R., Blencowe, N., Boutron, I., Cates, C., Cheng, H.-Y., Corbett, M., Eldridge, S., . , Hernán, M., Hopewell, S., Hróbjartsson, A., Junqueira Dr, J., Üni P, K., JJ. , Lasserson, T., Li, T., Mcaleenan, A., Reeves, B., Shepperd, S., Shrier, I., Stewart, L., Tilling, K., White, I., Whiting, P. & Higgins, J. 2019. Rob 2: A revised tool for assessing risk of bias in randomised trials. . *BMJ,* 366.

Stredova, M., Stepanov, A., Studnicka, J., Nekolova, J. & Jiraskova, N. 2019. Ranibizumab in macular oedema secondary to branch retinal vein occlusion - 24 months of treatment. *Ceska a Slovenska Oftalmologie,* 75**,** 190-198.

Tadayoni, R., Waldstein, S. M., Boscia, F., Gerding, H., Gekkieva, M., Barnes, E., Das Gupta, A., Wenzel, A. & Pearce, I. 2017. Sustained benefits of ranibizumab with or without laser in branch retinal vein occlusion: 24-month results of the brighter study. *Ophthalmology,* 124**,** 1778-1787.

Tsagkataki, M., Papathomas, T., Lythgoe, D. & Kamal, A. 2015. Twenty-four-month results of intravitreal bevacizumab in macular edema secondary to branch retinal vein occlusion. *Seminars in Ophthalmology,* 30**,** 352-359.

Van Aken, E., Favreau, M., Ramboer, E., Denhaerynck, K., Macdonald, K., Abraham, I. & Brie, H. 2020. Real-world outcomes in patients with diabetic macular edema treated long term with ranibizumab (vision study). *Clin Ophthalmol,* 14**,** 4173-4185.

Volkmann, I., Knoll, K., Wiezorrek, M., Greb, O. & Framme, C. 2020. Individualized treat-and-extend regime for optimization of real-world vision outcome and improved patients' persistence. *BMC Ophthalmology,* 20**,** 122.

Who 2021. World report on vision. *WHO Reports.*

Wu, L., Arevalo, J. F., Berrocal, M. H., Maia, M., Roca, J. A., Morales-Canton, V., Alezzandrini, A. A. &

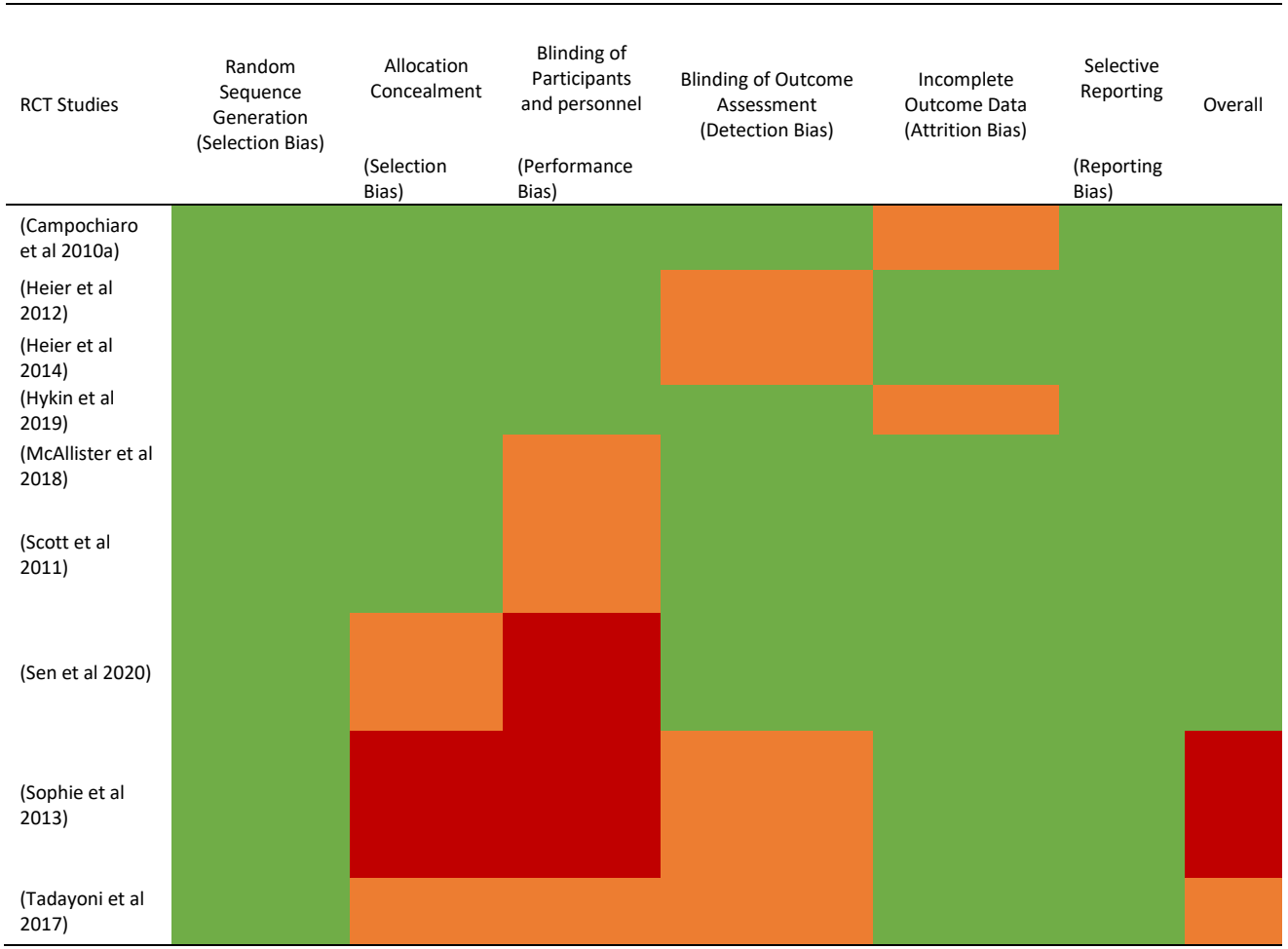
Diaz-Llopis, M. J. 2009. Comparison of two doses of intravitreal bevacizumab as primary treatment for macular edema secondary to branch retinal vein occlusions: Results of the pan american collaborative retina study group at 24 months. *Retina,* 29**,** 1396-403.

Yorston, D. 2014. Intravitreal injection technique. *Community Eye Health,* 27**,** 47.

Ziemssen, F., Feltgen, N., Holz, F. G., Guthoff, R., Ringwald, A., Bertelmann, T., Wiedon, A., Korb, C. & Group, O. s. 2017. Demographics of patients receiving intravitreal anti-vegf treatment in real-world practice: Healthcare research data versus randomized controlled trials. *BMC Ophthalmol,* 17**,** 7.

APPENDIX

Appendix A - Cochrane Risk of Bias Tool for RCTs (Higgins et al., 2011)



Appendix B - Joanna Briggs Critical Appraisal Tool for Cohort studies (Munn Z et al., 2020)

Cohort Studies	Were patient demographic characteristics clearly described?	Was there clear reporting of clinical information of the participants?	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Was the intervention(s) or treatment procedure(s) clearly described?	Were the outcomes or follow up results of cases clearly reported?	Were adverse events (harms) or unanticipated events identified and described?	Was statistical analysis appropriate?	Overall
(Abdallah et al 2019)									
(Bajric et al 2015)									
(Blanc et al 2018)									
(Busch et al 2018)									
(Chatziralli et al 2018)									
Chatziralli et al (2017)									
(Chittajallu et al 2018)									
(Costa et al 2021)									
(Farinha et al 2016)									
(Gale et al 2020)									
(Guichard et al 2017)									
(Hosogi et al 2019)									
(Iftikar et al 2019)									
(Lida-Miwa et al 2019)									
(Lo et al 2020)									
(Ozkaya et al 2018)									
(Sophie et al 2013)									
(Spooner et al 2019)									
(Tsagkataki et al 2015)									

Appendix C - CASP tool for risk of bias assessments for case studies (CASP, 2018)

Case Series	Address a clearly focused issue?	Was the cohort recruited accurately?	Was the exposure measured to minimise bias?	Was the outcome measured to minimise bias?	Had authors identified all important confounding factors?	Taken account of the confounding factors in design and/or analysis?	Follow up of subjects complete ?	Was the follow up of subjects long enough?	Do you believe the results?	Can the results be applied to the local population ?	Do the results of this study fit with other evidence?	What are the implications of this study for practice?	Overall
(Blin et al 2018)												Ranibizumab is effective.	
(Brown et al 2014)												Ranibizumab in CRVO = improved vision	
(Calugaru and Calugaru 2015)												"IVB = sustained vision over 3 years"	
(Campochiaro et al 2014)												"LTO with ranb are excellent'	
(Hikichi et al 2014)												IVB is beneficial at 2 years	
(Horner et al 2020)												Combination therapy is effective	
Inagaki et al 2019)												"IVR + PRN gave good visual outcome at month 24"	
(Khurana et al 2019)												TAE aflibercept at 2 years = improvement	
(Korobelnik et al 2016)												Dex implant = safe	
(Larsen et al 2014)												BCVA gains -ranb at 2 years	
(Lee et al 2014)												IVB, IVTA or IVA = improvement in BCVA at 2 years.	
(Loukiano et al 2016)												Bev injections = long term BCVA improvement at 2 years	
(Maggio et al 2020)												IVR/Dex effective at LTO BCVA and CRT	
(Mansour et al 2018)												BCVA improves over 2 years with IVA	
(Risard et al 2011)												Ranibizumab LTO = good	
(Sakanishi et al 2021)												IVA effective at 2 years for BRVO	
(Stredova et al 2019)												Ranibizumab = positive LTO	
(Volkmann et al 2020)												VA improves with TAE anti-VEGF.	
(Wu et al 2009)												IVB is effective at 2 years.	