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Health Economics
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NOVARTIS

Bevacizumab (Avastin) for Macular Edema Secondary to RVO

Review of Evidence on Clinical Effectiveness and Safety from Non-Randomised Controlled Trials

Draft Report
Ver 2.0

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C O N S O R T I U M

Contents

Executive Summary

1. INTRODUCTION

This review was undertaken to assess evidence on the clinical effectiveness, safety and health-related quality of life of bevacizumab (Avastin) for the treatment of macular edema secondary to retinal vein occlusion (RVO), as investigated in non-randomised studies, to inform a Health Technology Assessment submission for Lucentis for which bevacizumab may be a comparator.

2. METHODS

The extensive searches conducted in a preliminary review had identified 64 potentially relevant records for inclusion in this review, based on the titles and abstracts (Glanville 2010). The full papers were then assessed for relevance. Relevant studies were judged to be those which met the following criteria:

- Participants: adults with macular edema caused by RVO, both branch and central;
- Interventions: bevacizumab (Avastin) administered by intravitreal (IVT) injection or intravenously, either alone or in combination with other therapies;
- Comparators: pharmaceutical agents (e.g. ranibizumab, pegaptanib sodium, triamcinolone acetonide, dexamethasone); other treatments (e.g. laser photocoagulation, surgery); best supportive care or no treatment;
- Outcomes: visual acuity (best-corrected visual acuity (BCVA) where specified) in the treated eye, measured on any scale; adverse effects; health-related quality of life (HRQoL);
- Study designs: for clinical effects - controlled clinical trials and before-after studies; for adverse effects and health-related quality of life (HRQoL) - controlled clinical trials, before-after studies, prospective observational studies and registers of treated patients;
- Correspondence reporting new results (i.e. results from studies as yet unpublished).

Retrospective studies and analyses were excluded.

Data were extracted from studies into detailed tables for each clinical outcome (VA/BCVA, ocular structural measurements) and adverse effects (ocular and systemic). The quality of the studies was appraised using checklists suggested by the Centre for Review and Dissemination, modified to assess the strength of evidence from observational studies assessing effectiveness.

3. RESULTS

Sixty-four reports were assessed in detail for eligibility according to the selection criteria. Of these, 21 reports (corresponding to 18 studies) provided evidence on the effect of bevacizumab in the treatment of RVO, as defined in the inclusion criteria. The included studies appeared to comprise nine before-and-after studies and nine case series; no controlled trials were identified. The breakdown according to study design, *as described by the authors*, was:

- four prospective studies (Costa 2007, Kondo 2009, Park 2009, Sivkova 2010)
- one prospective non-randomised study (Rensch 2009a)
- one prospective clinical trial/uncontrolled study (Funk 2009, Kriechbaum 2008, Kriechbaum 2009, Prager 2009)
- one non-randomised uncontrolled study (Rensch 2009b)
- nine case series/consecutive cases (Gutierrez 2008, Hung 2010, Jaissle 2009, Kreutzer 2008, Pai 2007, Pournaras 2008, Priglinger 2007, Stahl 2007, Yamashiro 2010)
- two studies of unspecified design (Hoeh 2009, Moschos 2008).

No registry studies were identified. All of the reports had been published from 2007 onwards.

Nine studies were eligible for the review of clinical effects and seventeen for the review of adverse effects; no studies were identified that presented relevant data on HRQoL.

Based on the methods reported, the quality of the studies was judged to be low. The majority of studies (14/18) had explicit inclusion criteria. The wide variation in reporting of the baseline characteristics of the participants meant it was generally unclear whether the studies could be considered to be based on a representative sample from a relevant population. The absence of participant detail made it difficult to assess whether the participants were at a similar point in terms of disease progression. Where applicable, all studies reported data to enable an assessment of whether the duration of follow-up was long enough to capture adverse effects arising from bevacizumab administration. By virtue of the tests used to evaluate VA and ocular structural measures we judged that all studies used objective and subjective criteria to assess the clinical effects outcomes.

The major study limitations, as described by the authors, were:

- small sample sizes and lack of a sample size calculation that would allow confirmation of a pre-planned hypothesis;
- the absence of a control group: none of the studies found included a control arm
- and limited follow-up: of 6 to 12 months.

The studies were conducted in diverse populations, with participants presenting with macular edema secondary to RVO of varying type and severity:

- Seven studies included patients with BRVO (Gutierrez 2008, Jaissle 2009, Kondo 2009, Kreutzer 2008, Park 2009, Rensch 2009a, Yamashiro 2010),
- four studies included patients with CRVO (Moschos 2008, Pournaras 2008, Priglinger 2007, Rensch 2009b)

- seven studies included a mixture of patients: one study with central and hemicentral RVO (Costa 2007) and six studies with both BRVO and CRVO patients (Funk 2009, Hoeh 2009, Hung 2010, Kriechbaum 2008, Kriechbaum 2009, Pai 2007, Prager 2009, Sivkova 2010, Stahl 2007).

3.1 Clinical Effects

Nine studies (12 reports) were eligible for the review of clinical effects (Costa 2007, Funk 2009, Hoeh 2009, Kondo 2009, Kriechbaum 2008, Kriechbaum 2009, Moschos 2008, Park 2009, Prager 2009, Rensch 2009a, Rensch 2009b, Sivkova 2010). Within this review, results for clinical effects were presented with studies grouped by type of RVO.

BRVO

Six studies (7 reports) evaluated clinical effects in patients with BRVO (Hoeh 2009, Kondo 2009, Kriechbaum 2008, Park 2009, Prager 2009, Rensch 2009a, Sivkova 2010). All evaluated visual function and measures of ocular thickness. Visual acuity was assessed using Snellen charts (2 studies), the Early Treatment Diabetic Retinopathy Study (ETDRS) (2 studies), a standard Japanese decimal VA chart (1 study), or the test was not reported (1 study); VA or BCVA was reported in terms of lines, letters or the logarithm of the minimum angle of resolution (log MAR). All six studies measured ocular thickness using ocular coherence tomography (OCT). None of the studies evaluated contrast sensitivity.

The effects of treatment with bevacizumab were variable. Three studies reported statistically significant improvements in BCVA and log MAR, compared with baseline, at 6 months and up to a mean of 59 weeks for patients receiving multiple injections (Hoeh 2009, Kriechbaum 2008, Prager 2009, Rensch 2009a). Two studies reported significant improvements in BCVA at 1 month (Kondo 2009) and 6 weeks (Sivkova 2010) for patients also receiving multiple injections, but no significant changes beyond these times, although initial improvements were stable for 12 months (Kondo 2009) and 16 weeks (Sivkova 2010). The remaining study compared BCVA log MAR in responders and non-responders to a single injection of bevacizumab, none of whom had received prior treatment for macular edema (Park 2009). A non-responder was defined as showing persistent macular edema at 6 weeks after injection, based on a <20% reduction of central macular thickness from baseline measurement and vision improvement by <0.3 log MAR. Despite similar baseline log MAR in the two groups, significant improvements in log MAR were observed in responders after 6 weeks (Park 2009).

The majority of studies reported significant reductions in macular thickness from baseline. Three studies observed significant reductions in central retinal thickness (CRT) in patients with ‘significant’ (not defined) macular edema or macular edema involving the foveal centre who were given multiple injections: one at last visit (mean follow-up 59 weeks) (Hoeh 2009), one at all examinations during the 6-month study (Rensch 2009a) and one at 6 and 12 months (Kriechbaum 2008, Prager 2009. Central macular thickness (CMT) was significantly reduced following a single injection of bevacizumab in responders compared with non-responders after 6 weeks (Park 2009), while decreases in CMT observed at 4 and 8 weeks in patients given multiple injections were stable for up to 16 weeks (Sivkova 2010). The only study to evaluate foveal thickness (Kondo 2009) observed significant reductions in foveal

thickness at 1 and 3 months for patients treated with 1-4 injections of bevacizumab, but no significant changes from then onwards up to 12 months. At 12 months, 29 eyes (50%) showed a decrease in foveal thickness of ≥30% and no eyes showed an increase in thickness of ≥30%.

Where reported, the main factors correlated with improved vision were baseline VA (Hoeh 2009, Kondo 2009, Kriechbaum 2008), patient age (Hoeh 2009, Kondo 2009) and CRT (Hoeh 2009, Rensch 2009a).

CRVO

Five studies (6 reports) evaluated clinical effects in patients with CRVO (Hoeh 2009, Kriechbaum 2008, Moschos 2008, Prager 2009, Rensch 2009b, Sivkova 2010). All evaluated visual function and measures of ocular thickness. VA was assessed using Snellen charts (2 studies), the ETDRS (2 studies), or the test was not reported (1 study); VA or BCVA was reported in terms of lines, letters or log MAR. All five studies measured ocular thickness using OCT. None of the studies evaluated contrast sensitivity.

The effects of treatment with bevacizumab were variable. Two studies (Hoeh 2009, Rensch 2009b) reported significant improvements in VA for patients naïve to treatment for macular edema who were given multiple injections. Gains of at least 3 lines in BCVA were observed in 12 patients (44.4%) at the last visit (61 weeks) (Hoeh 2009), and in 14 patients (56%) at 6 months (Rensch 2009b). Six patients (24%) did not show any improvement in VA at 1, 3 or 6 months (Rensch 2009b). Two studies reported non-significant increases in BCVA (Snellen and log MAR) from pre-treatment values at 1 and 3 months (Moschos 2008, and 6 and 12 months (Kriechbaum 2008, Prager 2009) in patients with non-ischemic CRVO given 1-3 injections. The remaining study (Sivkova 2010) reported fluctuations, but not improvements in BCVA, in a 16-week study of patients given multiple injections.

The majority of studies reported significant reductions in macular thickness from baseline. Three studies observed significant reductions in CRT in patients with cystoid macular edema and/or macular edema involving the foveal centre who were given multiple injections: one study at last visit (mean follow-up 61 weeks) (Hoeh 2009), one study at all examinations during the 6-month study (Rensch 2009b) and the EUDRACT study at 12 months (Prager 2009). 6-month results for the EUDRACT study showed a non-significant decrease in CRT (Kriechbaum 2008). CMT and foveal thickness were both evaluated in only one study (Sivkova 2010, Moschos 2008). The significant decrease in CMT observed at 4 weeks in patients given multiple injections was stable for up to 16 weeks (Sivkova 2010), while significant reductions in foveal thickness were observed in a 3-month study of patients who had been treated with a single injection (Moschos 2008). From our calculations (there were some discrepancies in the original paper) foveal thickness at 1 and 3 months was approximately 43% lower than the pretreatment value.

One study found a correlation between increased VA and decrease in macular thickness (Rensch 2009b), while EUDRACT found no correlation between improved BCVA and patient age, baseline VA, CRT, or duration of thrombosis.(Kriechbaum 2008).

Mixed/Other RVO

Four studies (7 reports) described mixed populations of patients, but only two evaluated the overall clinical effects: one reported results for patients with central or hemicentral RVO (Costa 2007) and the EUDRACT study reported results for patients with BRVO or CRVO (Funk 2009, Kriechbaum 2008, Kriechbaum 2009, Prager 2009). Both studies evaluated visual function and measures of ocular thickness. VA was assessed using the ETDRS or a modified ETDRS, with BCVA reported in terms of lines, letters or log MAR. Ocular thickness was measured using OCT. Neither study evaluated contrast sensitivity.

Both studies reported improvements in VA with bevacizumab. In a 25-week study of patients with ischemic central or hemicentral RVO who had not undergone prior treatment and received at least one injection of bevacizumab, none of the patients showed a reduction in BCVA lines or log MAR (Costa 2007). Forty-six patients (66.7%) achieved a gain of at least 3 lines in VA at 25 weeks (Costa 2007). EUDRACT found significant improvements in BCVA at 1, 3, 6 and 12 months in patients with non-ischemic BRVO or CRVO treated with multiple injections (Kriechbaum 2008, Kriechbaum 2009, Prager 2009); the fourth EUDRACT report described fluctuations in BCVA over 15 months (Funk 2009).

Findings in relation to macular thickness were variable. The most favourable reductions in CMT were observed at 1 and 6 weeks, after which CMT increased compared with 6-week data (Costa 2007). Changes in OCT examinations at 6 and 18 weeks suggested that the maximum effect of bevacizumab may be achieved at least up to 6 weeks after injection. EUDRACT reported mixed results for patients with clinically significant or cystoid macular edema involving the foveal centre: fluctuations in CRT over 15 months (Funk 2009); significant and stable decreases in CRT, centre subfield thickness and mean retinal thickness over 12 months (Kriechbaum 2009); an initial decreases in CRT which was maintained for 3 months, then followed by a non-significant increase in CRT at 6 months upon retreatment (Kriechbaum 2008); and a significant decrease in CRT at 12 months (Prager 2009).

A correlation was observed between improved BCVA and decreased CRT.

3.2 Adverse Effects

Seventeen studies (20 reports) were eligible for the review of adverse effects. In general, adverse effects were poorly reported, the data were sparse, and the majority of studies did not appear to have conducted a comprehensive, objective assessment of adverse events, An objective assessment might be expected to focus on eye disorders arising from unlicensed IVT use of bevacizumab, as described in the product information supplied by the European Medicines Agency, in addition to effects of a more systemic nature. Ideally, the methods section of a study report should identify the principal adverse effects of interest, and outline the techniques or analytical methods used to monitor them. 14 reports did refer to the monitoring or recording of adverse effects within their methods: seven monitored specific adverse effects, sometimes as secondary outcomes, two monitored adverse effects in general (local and/or systemic), and five stated that they measured intraocular pressure. Only one study defined the adverse effects of interest (Priglinger 2007). This review presents the results for ocular adverse events and systemic adverse events.

Ocular Adverse Effects

All 17 studies provided limited data on ocular adverse effects. Complications and side effects of treatment were typically infrequent or absent, and the majority of studies either provided statements to this effect or reported zero cases of specific events.

Six studies, with duration of follow-up ranging from at least 1 month to 1 year, described ocular-related events in patients with BRVO alone (Gutierrez 2008, Jaissle 2009, Kondo 2009, Kreutzer 2008, Rensch 2009a, Yamashiro 2010). One study was a report of 14 cases of endophthalmitis arising from the use of bevacizumab for various ocular diseases, of which 3 patients (3 eyes) had BRVO (Yamashiro 2010). Conjunctive hyperemia and moderate inflammation were observed in 2 of these 3 eyes with endophthalmitis. The remaining studies made a statement regarding the absence of procedural- or drug-related complications, or ocular or local side effects. One study also reported no cases of raised IOP or clinically significant cataract (Rensch 2009a), and another no cases of endophthalmitis, retinal detachment or neovascular complications (Jaissle 2009).

Four studies, with duration of follow-up ranging from 3 months to 1 year, described ocular-related events in patients with CRVO alone (Moschos 2008, Pournaras 2008, Priglinger 2007, Rensch 2009b). One study reported a single case of localised hyperemia at the injection site (Pournaras 2008) (n=8). The other three studies reported the absence of specific adverse effects: no cases of raised IOP (Moschos 2008), increased IOP or clinically significant cataract (Rensch 2009b), or endophthalmitis, retinal tears, lens trauma or rubeosis (Priglinger 2007). All four studies made a statement regarding the absence of ocular or drug-related adverse effects.

Seven studies with duration of follow-up ranging from 9 weeks to up to 15 months, described ocular-related events in populations of mixed RVO type: central or hemicentral RVO (Costa 2007) and BRVO or CRVO (Funk 2009, Hoeh 2009, Hung 2010, Kriechbaum 2008, Kriechbaum 2009, Pai 2007, Prager 2009, Sivkova 2010, Stahl 2007).

The only study of patients with central and hemicentral RVO reported 3 cases of conjunctival hyperemia and subconjunctival hemorrhage at the injection site and no significant changes in IOP or lens status (Costa 2007) (n=7). The remaining studies reported no observations of the following: inflammation/uveitis (Costa 2007, Hung 2010, Kriechbaum 2008, Pai 2007, Prager 2009), retinal detachment (Hung 2010, Kriechbaum 2008, Pai 2007, Prager 2009, Stahl 2007), endophthalmitis (Hung 2010, Kriechbaum 2008, Pai 2007, Prager 2009, Stahl 2007), cataract (Pai 2007, Prager 2009, Stahl 2007); increased IOP (Pai 2007, Stahl 2007), neovascular complications (Hoeh 2009, Prager 2009), central retinal occlusion (Stahl 2007), glaucoma (Hung 2010), retinal tears (Pai 2007) and vitreous hemorrhage (Hung 2010). All but the EUDRACT study (Funk 2009) made general statements about the absence of drug- or injection-related side effects, ocular toxicity, and ocular or local adverse effects, short-tem or severe.

Systemic Adverse Effects

Thirteen studies provided limited data on systemic adverse effects; all reported an absence of such events. The majority of studies either provided statements to this effect or reported zero cases of specific events.

The four studies that considered adverse systemic events in patients with BRVO alone made statements concerning the general lack of such effects. No obvious or serious systemic adverse events (Gutierrez 2008, Jaissle 2009, Kondo 2009) or injection-related side effects (Kreutzer 2008) were observed during the duration of the studies (6 months to 1 year).

Three studies made statements about the general lack of adverse effects in patients with CRVO alone. No patients showed clear systemic side effects (Moschos 2008) and no adverse effects (Priglinger 2007) or serious adverse effects (Pournaras 2008) were observed over 3-6 months' follow-up.

Six studies (9 reports) commented on adverse effects in patients of mixed RVO type. No significant changes in blood pressure were observed during the 25-week study of patients with central or hemicentral RVO, and no serious-drug related adverse effects were seen (Costa 2007). The remaining 5 studies made statements concerning the absence of systemic adverse effects (Funk 2009, Hung 2010, Kriechbaum 2008, Pai 2007, Prager 2009) or side effects in general (Kriechbaum 2009, Sivkova 2010, Stahl 2007) over the duration of the studies (9 weeks to up to 15 months). Two studies recorded zero cases of thromboembolic events (Funk 2009, Hung 2010, Kriechbaum 2008, Prager 2009), EUDRACT reported systemic hypertension and kidney failure (Prager 2009), and Hung reported cardiovascular accidents (Hung 2010).

Health-Related Quality Of Life (HRQoL)

No non-randomised studies were identified that assessed HRQoL. None of the studies eligible for the reviews of clinical effects and adverse effects reported HRQoL.

4. CONCLUSIONS

No controlled studies of bevacizumab in the treatment of macular edema secondary to RVO were identified. The uncontrolled studies identified used various research designs: these include what appear to be before-and-after studies with multiple measurements, where the patients' visual acuity was measured before they received intervention and at several time points after (thus assessing their response to the treatment), and what the authors described as case series. Neither of these study designs are ideal sources of data as determined by published hierarchies of evidence. In general, the included studies had small sample sizes (maximum 61 eyes) and a short duration of follow-up (maximum 12 months), and suffered from poor, inconsistent reporting of methodology, participant characteristics and outcome measures. Differences between the studies in terms of their reporting, and interventions,

participants and study designs, precluded meta-analysis and hindered comparisons between studies within the narrative synthesis.

The quality of the evidence presented is likely to be low given the inherent biases arising from the use of non-randomised study designs. The results of the studies should therefore be interpreted with caution.

In patients with BRVO, bevacizumab typically resulted in significant increases in VA and reductions in measures of retinal thickness, compared with pre-treatment values, although some initial benefits were not improved on over time. The effects of treatment in patients with CRVO were more variable, with significant improvements or fluctuations in VA being observed compared with pre-treatment values; macular thickness was typically reduced. Treatment with bevacizumab resulted in significant improvements in VA in both studies of patients with mixed RVO, but variable effects on macular thickness: one study found a short-term benefit in patients with central and hemicentral CRVO while the other, which was published in four separate articles, reported mixed results in patients with BRVO or CRVO.

Data on adverse effects were limited and few studies appear to have conducted a comprehensive, objective assessment of such events, although 14 of the 20 reports stated their intention to record or monitor adverse effects within their methods; only one study defined the targeted adverse events. Apart from one report describing cases of endophthalmitis in patients treated with bevacizumab for various ocular conditions, of which 3 patients had BRVO, complications or adverse effects of treatment were typically infrequent or absent, and the majority of studies either made statements to this effect or reported zero cases of specific events. Where reported, hyperemia, inflammation and subconjunctival hemorrhage were the only ocular adverse effects observed, but such cases were few in number; no systemic adverse effects were recorded. No studies were identified that assessed HRQoL.

Better controlled studies are needed to investigate the effectiveness of bevacizumab. Better and more consistent reporting is needed, in particular of participant characteristics; ideally, there should be minimum requirements for the type and level of information to be presented. This should facilitate appropriate comparisons and allow more robust and valid conclusions to be drawn, and also enable an assessment of the generalisability of the results. Improvements in the surveillance and formal reporting of adverse events are needed. Ideally, this would take the form of comprehensive, objective assessments of adverse events, rather than the more subjective, sporadic reporting that seems to occur at present.

List of Abbreviations

AAO	American Academy of Ophthalmologists
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
BRVO	branch central retinal occlusion
CAD	coronary artery disease
CI	confidence interval
CMT	central macular thickness
CRT	central retinal thickness
CRVO	central retinal vein occlusion
CSME	clinically significant macular edema/oedema
CST	central subfield thickness
CVD	cerebrovascular disease
DM	diabetes mellitus
DMO	diabetic macular edema
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescence angiography
FFA	fundus fluorescein angiography
GLA	glaucoma
HC	hypercholesterolemia
HRQoL	health-related quality of life
HT	hypertension
IOP	intraocular pressure
IVT	intravitreal
log MAR	logarithm of the minimum angle of resolution
MAR	minimum angle of resolution
MFERG	multifocal electroretinography
MRT	mean retinal thickness
NR	not reported
OCT	optical coherence tomography
PEDF	pigment epithelium-derived factor
PERG	pattern electroretinogram
PRP	panretinal photocoagulation
QoL	quality of life
RCTs	randomised controlled trials
RVO	retinal vein occlusion
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
VA	visual acuity
VEGF	vascular endothelial-growth factor

Section 1: Introduction

1.1 OBJECTIVES

This review was undertaken to inform Novartis' Health Technology Assessment (HTA) submission for Lucentis for which bevacizumab (Avastin) is a potential comparator. It aimed to assess evidence on the clinical effectiveness and safety of bevacizumab for the treatment of macular edema secondary to retinal vein occlusion (RVO), as investigated in non-randomised studies; potentially relevant studies had been identified through a preliminary review of bevacizumab for the treatment of diabetic macular edema (DME), macular edema caused by RVO, and wet-age-related macular degeneration (AMD) (Glanville 2010). Any evidence on health-related quality of life (HRQoL) found during the course of this review was also assessed.

1.2 BACKGROUND

Bevacizumab (Avastin) is a humanised monoclonal antibody fragment that binds selectively to human vascular endothelial growth factor (VEGF), a protein which is found on the lining of blood and lymph vessels in the body. VEGF stimulates the formation of blood vessels (angiogenesis) within tumours; these blood vessels provide the tumour with nutrients and oxygen with which to develop. Once bound to VEGF bevacizumab inhibits angiogenesis and, since the cancer cells are unable to develop their own blood supply and are starved of nutrients and oxygen, tumour growth is slowed down (European Medicines Agency).

Bevacizumab is licensed for the treatment of advanced cancer in the large bowel, metastatic breast cancer, advanced non-small cell lung cancer and advanced kidney cancer, but is not licensed for any ophthalmic indication, although it has been subject to extensive investigation (Bevacizumab (Avastin®, Roche) 2010).

Macular edema is the swelling of the retina as a result of seepage (exudation) and accumulation of extracellular fluid and proteins in the macula due to the breakdown of the blood-retina barrier and an increase in vascular permeability (Parravano 2009, Girach 2007). Since the macula is the central part of the retina responsible for colour vision and perception of fine detail, macular edema can lead to severe visual impairment in the affected eye (National Institute for Health and Clinical Excellence 2010).

Retinal vein occlusion is a common retinal vascular disease in which macular edema may develop, leading to severe visual loss (National Institute for Health and Clinical Excellence 2010, Braithwaite 2010). It occurs when the central retinal vein – the blood vessel that drains the retina - or one of its branches becomes blocked. Hence, the main two types of RVO are central RVO or branch RVO, as classified by the anatomy of the occluded vein. This occlusion can lead to the development of macular edema and varying levels of ischemia (Retinal Vein Occlusion 2010). Central RVO can be further sub-categorized

according to the degree of ischemia produced: non-ischemic (venous stasis retinopathy) and ischemic (hemorrhagic retinopathy) (Spires 1993). The non-ischemic type may resolve completely without any complications or progress to the ischemic type, which is more severe (National Institute for Health and Clinical Excellence 2010).

The International Eye Disease Consortium report estimated that 13.9 million people worldwide are affected by branch RVO and 2.5 million by central RVO, (First report on worldwide prevalence of retinal vein occlusion 2010) but no prevalence or incidence data has been identified for England and Wales (National Institute for Health and Clinical Excellence 2010). Prevalence is similar in men and women and increases with age. Other risk factors include hypertension, hyperlipidemia, diabetes mellitus, hyperviscosity, hypercoagulability, thrombophilia, glaucoma and trauma (National Institute for Health and Clinical Excellence 2010, Retinal Vein Occlusion 2010, First report on worldwide prevalence of retinal vein occlusion 2010).

Patients with RVO may receive laser photocoagulation but more frequently receive best supportive care. Pharmacological therapies such as intravitreal (IVT) injections of bevacizumab or intravitreal triamcinolone acetonide may also be used experimentally and off-license.

Novartis has requested a systematic review to assess evidence on the clinical effectiveness, safety and health-related quality of life of bevacizumab for the treatment of macular edema secondary to retinal vein occlusion (RVO), as investigated in non-randomised studies. This systematic review may be used to inform Novartis' Health Technology Assessment submission for ranibizumab (Lucentis): the NICE scope includes bevacizumab as a comparator for ranibizumab.[1]

[1] National Institute for Health and Clinical Excellence Final scope for the appraisal of ranibizumab for the treatment of macular oedema caused by retinal vein occlusion (RVO). London: NICE: March 2011.

Section 2: Methods

This systematic review of clinical effectiveness, adverse effects and health-related quality of life was conducted according to a protocol, which specified the identification, selection, data extraction and synthesis of research evidence as summarized below.

2.1 RESEARCH QUESTION

This review identified, selected and assessed non-randomised studies identified from a systematic search (Glanville 2010). The inclusion criteria are described in detail below.

2.1.1 Participants

Eligible study participants were adults with macular edema caused by RVO, both branch and central.

We also included studies reporting results for mixed populations if the outcome data for patients with macular edema caused by RVO and patients with other eye disorders were sufficiently disaggregated.

2.1.2 Interventions

Eligible interventions were bevacizumab (Avastin) given by intravitreal (IVT) injection or intravenously, either alone or in combination with other therapies.

2.1.3 Comparators

Eligible comparators were:

- Pharmaceutical agents such as ranibizumab (Lucentis), pegaptanib sodium (Macugen), IVT triamcinolone acetonide and dexamethasone;
- Other treatments including laser photocoagulation or surgery;
- Best supportive care or no treatment.

2.1.4 Outcomes

Eligible outcomes were:

- Visual acuity (VA) or best-corrected visual acuity (BCVA)[2] in the treated eye, as measured on any scale, e.g. ETDRS letters, logarithm of the minimum angle of resolution (log MAR);
- Adverse effects;
- Health-related quality of life (HRQoL).

2.1.5 Types of Study

Intervention studies and observational study designs were eligible for inclusion, as outlined below for each outcome of interest.

Study designs eligible for evidence on clinical effects were:

- Controlled clinical trials;
- Before-and-after studies[3].

Study designs eligible for evidence on adverse effects were:

- Controlled clinical trials;
- Before-and-after studies;
- Prospective observational studies;
- Registers of treated patients.

Study designs eligible for evidence on HRQoL were:

- Controlled clinical trials;
- Before-and-after studies;
- Prospective observational studies;
- Registers of treated patients.

Correspondence reporting new results (i.e. results from studies as yet unpublished) was also eligible for inclusion.

Retrospective studies and analyses were not eligible for inclusion because of the potential bias arising from retrospective approaches where the data were not necessarily collected for the purpose of the study or by the investigators of the retrospective study.

[2] BCVA is the visual acuity with the best glasses or contact lens prescription for an individual.

[3] For the purposes of this review, we consider a before-and-after study to be a single-arm intervention study, which has not been classified by its authors as a case series, with an apparent protocol, selection of participants, and measurement of predefined outcomes before and after administration of the intervention.

The literature search had excluded randomised studies (which had already been reviewed in previous reports), case reports, reviews, conference abstracts, and more general journal elements such as editorials, news items, routine correspondence and comments. It also excluded studies reported in languages other than English, including papers in languages other than in English but with an English abstract.

2.2 LITERATURE SEARCH

This review selected non-randomised studies identified from a search for non-randomised studies of the use of bevacizumab in DMO, macular edema caused by RVO, and wAMD (Glanville 2010). The searches were conducted in a range of databases indexing published research and were conducted using the strategies developed for the systematic review of randomised controlled trials that had been commissioned by Novartis. The searches were limited to human studies in the large bibliographic databases (such as MEDLINE), and to the English language; no date limits were applied. Full details of the search terms, search strategies and databases and resources searched are available in the original report (Glanville 2010).

2.3 STUDY SELECTION

Following the literature search, records were assessed for relevance by applying the eligibility criteria to the record titles and abstracts (1st pass).

Full paper copies of selected records were obtained. One reviewer screened the full text versions of these articles by applying the pre-defined inclusion criteria for participants, interventions, comparators, outcomes and study design (2nd pass). Any papers that did not clearly meet the inclusion criteria were discussed with other reviewers. Studies included at this stage are listed in Appendix A, while those excluded are tabulated, along with the reason for their exclusion, in Appendix B.

2.4 DATA EXTRACTION

One reviewer extracted the data from the full papers of each of the included studies. The extracted data related to the characteristics of the study and the study population and are outlined in Appendix C; the types of results to be extracted from the included studies for each main topic (clinical effects, adverse effects, HRQoL) are shown in Table 2.1.

Table 2.1: Outcome data extracted from included studies

Outcome/measure/result	Detail
Clinical effects	
Visual acuity	VA test Test conditions VA/BCVA reported Measure used Baseline/follow-up Mean change Specified loss/gain Proportion experiencing specified loss/gain Overall result
Contrast sensitivity	Test name Test conditions Measurement technique Baseline/follow-up Mean change
Ocular imaging measurements (macular structure)	Imaging technique Structural measure Units Baseline/follow-up Mean change Overall result
Adverse effects	
Ocular	Intraocular pressure (IOP) Endophthalmitis Retinal tears Retinal detachment Hemorrhage Hyperemia (red eye) Loss of vision Pain Irritation Inflammation Other
Systemic	Event Number (%) experiencing event
Health Related Quality of Life	
Quality of life (visual function and patient satisfaction)	Instrument Domain Baseline/ follow-up Overall

2.5 QUALITY ASSESSMENT

Tools such as the Downs and Black instrument (Downs 1998) and the Newcastle-Ottawa Quality Assessment Scale (Wells 2010) provide an overall numerical score which may be used to distinguish high and low quality studies. However, using scores to assess quality is problematic since the validity and reliability of developed scales has often not been established using standard techniques, and the scales can vary widely in terms of the weighting assigned to individual methodological items. In addition, they may not account for the direction of bias. (Centre for Reviews and Dissemination 2008) Given these limitations, it was considered inappropriate to assign a formal numerical quality score to the selected studies. We used a single checklist modified to assess the strength of evidence from observational studies assessing effectiveness (NHS Centre for Reviews and Dissemination

2001). One reviewer quality assessed each of the included studies. The following quality assessment/risk of bias questions were applied to the study designs encountered (uncontrolled studies and case series).

- Is the study based on a representative sample selected from a relevant population?
- Are the criteria for inclusion explicit?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
- If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?

In selecting a value for minimum follow-up we considered that a six week follow-up was the minimum requirement. One study (Matsuyama 2010) on the effect of a single IVT bevacizumab injection on blood levels of VEGF in patients with proliferative diabetic retinopathy found that bevacizumab penetrates into the retina, choroid, intraocular blood vessels and aqueous before entering quickly into the general blood circulation where it lowers the level of VEGF. Significant reductions in VEGF concentration were observed after 1 day, 7 days and even 1 month, suggesting that the effects of bevacizumab last at least 1 month. Other factors supporting our decision were the clearance time for bevacizumab - systematic elimination half-life of 18-20 days (European Medicines Agency 2010) - and the fact that in regimens involving multiple injections the injections are typically repeated at 6-week intervals.

2.6 DATA SYNTHESIS

The data were synthesised into narrative reviews. We explored the extent of methodological and clinical heterogeneity between the studies to assess the suitability of the data for statistical pooling.

Three reviews were envisaged:

- Clinical effects;
- Adverse effects;
- HRQoL.

Within the review of clinical effects, the studies were grouped by type of RVO and the main outcomes discussed for each:

- Branch retinal vein occlusion (BRVO);
- Central retinal vein occlusion (CRVO);
- Mixed/other RVO.

Within the review of adverse effects, ocular and systemic effects were discussed separately with studies grouped by RVO subtype.

Section 3: Results

The results of the systematic review are reported in this section as follows:

- Search results;
- Number of included studies;
- Description of included studies;
- Results of the review of clinical effects;
- Results of the review of adverse effects;
- Results of the review of HRQoL.

3.1 SEARCH RESULTS

The database searches yielded 308 records for RVO. Of these, 64 records were considered potentially relevant following assessment based on the title and abstract (Glanville 2010). These 64 records were assessed in more detail for eligibility for the review. The study identification flowchart is shown in Figure 3.1.

3.2 NUMBERS OF INCLUDED STUDIES

Twenty-one reports were relevant to the review. All reported some measure of clinical effect (12 met the study design criteria for inclusion in this review) and 20 reported on adverse effects; none reported on HRQoL. Although we identified 21 reports, four of these appear to report different outcomes for the same study, (registered on the European clinical database as EUDRACT-2005-003288-21.(Funk 2009, Kriechbaum 2008, Kriechbaum 2009, Prager 2009) Thus, while the total number of included reports is 21, the number of included studies is 18. The results are presented by study.

3.3 DESCRIPTION OF INCLUDED STUDIES

This section summarises the included studies in terms of their publication type and date, geographic location, study designs, interventions, sample sizes and duration of follow-up and populations. The overall aims and conclusions of the studies are presented in Appendix D. Table 3.2 presents a summary of the characteristics of the included studies.

3.3.1 Included Studies: Publication Type and Date

Twenty of the 21 publications were journal articles: Sivkova 2010 was a lecture published in a dedicated conference proceedings issue of a journal. The reports were all published from 2007 onwards (Table 3.1). The majority of reports (17/21; 81%) had been published in the last 3 years.

Figure 3.1: Study identification flowchart according to PRISMA

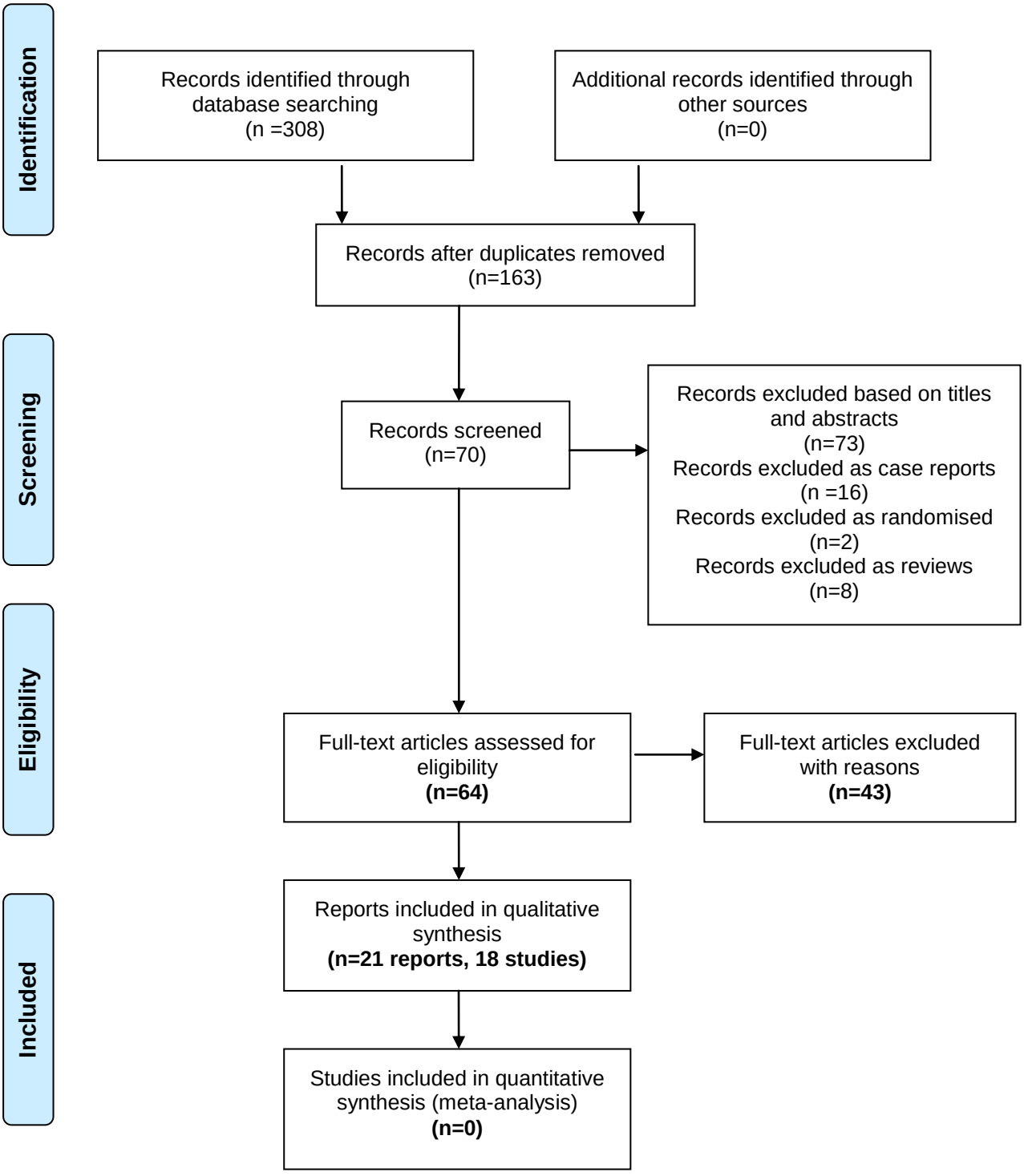

Table 3.1: Year of publication of included reports

Year of publication	Number of publications
2007	4
2008	5
2009	9
2010	3

3.3.2 Included Studies: Location

The 18 studies included in the review were widespread, coming from Austria (1), Brazil (1), Bulgaria (1), Germany (7), Greece (1), India (1), Japan (2), South Korea (1), Spain (1), Switzerland (1) and Taiwan (1). None of the research had been conducted in the UK.

Table 3.2: Characteristics of the included non-comparative studies.

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
BRVO alone									
Gutierrez 2008 Spain	Journal article	Case series	Patients aged ≥50 years; macular edema secondary to non-ischemic RVO; VA between 20/400 and 20/50 (Snellen equivalent).	12	12	Bevacizumab IVT injection (1.25 mg/0.5 mL) at baseline and once every 4 weeks if OCT indicated macular swelling.	6 months. Assessments at baseline and at 1, 4, 12 and 24 weeks, or on demand if the patient noted a decrease in VA.	visual acuity; adverse effects	Data tabulated for individual patients.
Jaissle 2009 Germany	Journal article	Case series	Duration of BRVO of 3 to 18 months; VA of ≤20/40 ; perfused macular edema; no hemorrhage in the fovea; no other disease that affects VA; no previous vitreoretinal surgery; no prior laser treatment to the macular area. For comparable inclusion criteria with another study, spontaneous resorption of hemorrhage was awaited in all patients, assuring that (theoretically) treatment with either IVT bevacizumab or	26	26	Bevacizumab IVT injection 1.25 mg/0.05 mL. Re-injection was considered at each follow-up visit. Treatment was discontinued if, despite having three consecutive injections, VA did not increase by ≥2 lines or macular edema did not decrease by ≥30%.	12 months. Examinations every 6 weeks up to 48 weeks.	visual acuity; adverse effects	The authors compared their findings with those of the BRVO Study Group, in order to evaluate whether bevacizumab or grid laser photocoagulation was more effective; the same inclusion criteria were used.

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
			grid laser photocoagulation would have been possible. Only patients with complete macular perfusion on FA were included.						
Kondo 2009 Japan	Journal article	Prospective study	Age ≥45 years, period from symptom onset to first injection ≤12 months, BCVA between 0.1 (20/200) and 0.6 (20/33), and foveal thickness ≥230 µm (by OCT).	50	50	Single bevacizumab IVT injection 1.25 mg/0.05 mL. Re-injection when macular edema reoccurred or if the results of the initial injection did not reach the level considered successful. Thirty-five eyes (70%) had the first injection within 12 weeks of the onset of symptoms.	12 months. Baseline and monthly evaluations.	visual acuity; adverse effects	Subgroup analyses on use of peripheral scatter photocoagulation to prevent the development of retinal neovascularization and vitreous hemorrhage; data for these not extracted. Methodology suggests before-and-after study.
Kreutzer 2008 Germany	Journal article	Case series	Patient eligibility with regard to diagnosis of macular edema after BRVO was confirmed from OCT images, fluorescein angiograms and	34	34	Bevacizumab IVT injections (1.25 mg/0.05 mL) on day 1 and 4 weeks thereafter. Only one eye was selected as the study eye.	6 months. Assessments at baseline and at 14 days, 6 weeks, and 3, 4 and 6 months after treatment.	visual acuity; adverse effects	Subgroup analysis according to whether patients were pretreated.

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
			fundus photographs.			Re-injections after the 2nd injection were based on treatment success, ineffectiveness or toxicity.			
Park 2009 South Korea	Journal article	Prospective study	Inclusion criteria for patients with recent onset BRVO were: post-injection follow-up >6 weeks; BCVA worse than 6/12; clinically detectable macular edema involving fovea confirmed by OCT; observation of perfusion status by FA; symptomatic duration ≤1 month; no history of prior treatment for macular edema associated with BRVO. Control group were healthy controls at the time of cataract surgery.	40 (excludes control group since not relevant to visual function)	40	Bevacizumab IVT injection 1.25 mg/0.05 mL.	Minimum 6 weeks (inclusion criterion). Examinations at baseline and monthly after bevacizumab injection.	visual acuity	Unclear study design. Not considered a comparative study in terms of clinical effects (i.e. VA) since control group only provided reference samples for growth factor levels; VA not assessed. Methodology suggests before-and-after study. Subgroup analysis according to response to treatment.
Rensch 2009a Germany	Journal article	Prospective non-randomised study	Significant macular edema as measured by OCT, loss of VA and leakage in FA.	21	21	3 bevacizumab IVT injections (1.5 mg) at 6-week intervals.	Not specifically reported. Mean follow-up was 6.3 months (6.2 ± 1.2 reported in	visual acuity; adverse effects	Methodology suggests before-and-after study.

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
							abstract). Examinations at baseline and at 1, 3 and 6 months after the first injection.		
Yamashiro 2010 Japan	Journal article	Consecutive cases	Not applicable: report of 14 cases of sterile endophthalmitis following injection of bevacizumab.	15 total; 3 with BRVO	19 total; 3 with BRVO	Bevacizumab IVT injection (1.25 mg/0.05 mL) from a single batch. Treatment was given within 1 week of the vial of bevacizumab (100 mg/4 mL) being aliquotted into 20 doses.	At least 1 month.	visual acuity; adverse effects	Study sample comprised patients with a variety of ocular diseases; only 3 patients with BRVO. Data tabulated or plotted on a graph for individual patients.
CRVO alone									
Moschos 2008 Greece	Journal article	Not specified	Not specifically stated but appears to be macular edema due to CRVO.	10	10	0.2 mL IVT injection of bevacizumab 1.25 mg/0.05 mL.	3 months. Evaluations at baseline and at 1 and 3 months after treatment.	visual acuity; adverse effects	Two masked evaluators assessed VA. Methodology suggests before-and-after study.
Pournaras 2008 Switzerland	Journal article	Case series	Presence of CRVO-associated macular edema with mean retinal thickness >300 µm associated with a VA <0.2 log MAR.	8	8	Bevacizumab IVT injection 1.25 mg/0.05 mL. Re-injection at monthly assessment if criteria met.	12 months. Baseline, 1 week, and monthly assessments. Results reported for the first 4 months of this ongoing study. Mean follow-up 3.25 months.	visual acuity; adverse effects	Ongoing study; only results for first 4 months reported.
Priglinger 2007	Journal article	Case series	Patient eligibility with regard to	46	46	Bevacizumab IVT injections	6 months.	visual acuity; adverse	Subgroup analysis for ischemic versus non-

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
Germany			diagnosis of macular edema after CRVO was confirmed by OCT, FA and fundus photographs. Patients were included independently of the size of the area of leakage, retinal thickness, VA, age, type of CRVO, or prior treatment performed beyond a period of 6 months.			(1.25 mg/0.05 mL) on day 1 and 4 weeks thereafter. Only one eye was selected as the study eye. If both eyes were eligible, the one with worse VA was selected for treatment. Re-injections after the 2nd injection were based on treatment success, futility or toxicity. Changes to the treatment (e.g. dose interruption and treatment discontinuation because of adverse events) were determined using criteria specified for targeted adverse events.	Assessments at baseline and at 14 days, 6 weeks, and 3, 4 and 6 months after treatment.	effects	ischemic CRVO.
Rensch 2009b Germany	Journal article	Non-randomised uncontrolled study	Significant macular edema as measured by OCT, loss of VA, and macular vessel leakage in FA.	25	25	3 bevacizumab IVT injections (1.5 mg) given at 6-week intervals.	6 months. Examinations at baseline and at 1, 3 and 6 months after the 1st injection.	visual acuity; adverse effects	Methodology suggests before-and-after study. Subgroup analysis conducted on 6 patients who did not

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
									show an improvement in VA at 1, 3 or 6 months after 1st injection.
Mixed/other RVO									
Costa 2007 Brazil	Journal article	Prospective study	Patients with macular edema associated with central or hemicentral RVO and log MAR (ETDRS) BCVA 0.4 or worse (Snellen equivalent, 20/50). The decrease in BCVA and macular edema (by OCT) had to be sustained (i.e. demonstrate no improvement) for at least 2 consecutive visits spaced 6-12 weeks apart. The last visit before baseline evaluation was considered the screening visit.	7	7	One IVT injection of 2.0 mg (0.08 mL) of bevacizumab at baseline. Retreatment at 12-week intervals if macular edema recurrence was documented by OCT.	6 months. Examinations at baseline and at 1, 6 and 12 (±1) weeks after each injection (weeks 1, 6, 12, 13, 18, 24, and 25).	visual acuity; adverse effects	Data also tabulated for individual patients. Methodology suggests before-and-after study.
EUDRACT (Funk 2009; Kriechbaum 2008; Kirechbaum 2009; Prager	4 journal articles	Prospective uncontrolled clinical trial	Clinically significant macular edema involving the fovea; duration of RVO >3 months before treatment initiation and without neovascularization;	28	29	3 bevacizumab IVT injections (variously reported in the papers as 1.25 mg/0.05mL and 1mg/0.04mL) at 4-week intervals (baseline and	Up to 15 months (mean 11 months). Baseline and evaluations at 1 day, 1 week, 1 month and then monthly evaluations thereafter.	visual acuity; adverse effects	Not considered a comparative study in terms of clinical effects (i.e. VA) since control group only provided reference samples for cytokine and growth factor levels; VA not assessed.

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
2009) Austria			BCVA measured by ETDRS charts at 2 m distance between 20/800 and 20/25 or no response to previous focal laser coagulation; CRT ≥250 µm due to intraretinal or subretinal edema, as measured by standard OCT imaging.			months 1 and 2). Retreatments started from visit 3 and were given at monthly visits if OCT showed edema or when loss of vision occurred. If retinal thickness did not fall below the 250- µm threshold after 6 consecutive injections of 1.25 mg/0.05 mL bevacizumab, the monthly dose was doubled to 2.5 mg (0.1 mL).			Subgroup analysis according to RVO type. Methodology suggests before-and-after study. Registered at the European clinical database (EUDRACT-2005-003288-21).
Hoeh 2009 Germany	Journal article	Not specified	Main inclusion criteria were macular edema involving the foveal centre with a minimum CRT at baseline of ≥250 µm.	61	61	Bevacizumab IVT injections 2.5 mg/0.1 mL. Re-injections only performed if OCT showed persistent or recurrent macular edema. The minimum interval between two injections was 6-8 weeks.	Minimum 6 months. Assessments at baseline and at 6- to 8-week intervals. Mean follow-up: Overall: 60±29 weeks (range: 25-128). BRVO group: 59±25 weeks CRVO group:	visual acuity; adverse effects	Subgroup analysis according to response to treatment. Methodology suggests before-and-after study.

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
							61±34 weeks		
Hung 2010 Taiwan	Journal article	Case series	Patients with macular edema secondary to perfused BRVO or CRVO, who had a CRT of >250 µm on OCT and a BCVA of 20/50 or worse.	25	25	Bevacizumab IVT injection 2.5 mg/0.1 mL. Repeated injections were performed on an as-needed basis when patients had persistent or recurrent macular edema.	Mean follow-up 6.5 months (range: 5.5–12). Assessments at baseline and 1 and 3 months after the first injection, and at the final visit	visual acuity; adverse effects	
Pai 2007 India	Journal article	Case series	Not specifically stated but appears to be patients with macular edema attributable to vein occlusion with vision less than 20/80. (Note: inclusion criteria used for the registered clinical trial are not reported here as the trial studies patients with a variety of retinal disorders). In their discussion, the authors stated that they included all patients who had vein occlusion with macular edema regardless of the ischemic	21	21	Single bevacizumab IVT injection 1.25 mg/0.05 mL.	3 months. Assessments at baseline and at 2 days and 1, 4, 8 and 12 weeks after injection.	visual acuity; adverse effects	Data also tabulated for individual patients. Study registered with ClinicalTrials.gov (NCT00403026). The registered clinical trial is studying 'Intravitreal bevacizumab for retinal disorders'. 8 patients in this study were included in an excluded record (Shetty. 2008). Record was excluded as the results were not reported separately for patients with macular edema due to RVO.

Author Year Country	Publication type	Study design (as described by authors)	Participant inclusion criteria	Total patients	Total eyes	Intervention	Length of study/ follow-up	Eligible outcomes for review	Comments
			status or duration of the symptoms.						
Sivkova 2010 Bulgaria	Journal conference proceedings (lecture)	Prospective study	Fundoscopically and angiographically diagnosed diabetic retinopathy, BRVO or CRVO with central macular edema >250µm (by OCT-SLO); BCVA ≤0.5; patient able to give informed consent.	127total; 31 with RVO	138 total; 31 with RVO	3 consecutive bevacizumab injections (1.25 mg/0.5 mL) given at 4-week intervals.	4 months. Results suggest examinations at baseline and 4, 8, 12 and 16 weeks after the first injection.	visual acuity; adverse effects	Study sample comprises patients with diabetic retinopathy, type 2 diabetes and RVO. Methodology suggests before-and-after study. Follow-up assessments unclear. Methods indicate examinations before 1st, 2nd and 3rd injections and 4 weeks after the last; this gives total duration of 12 weeks?
Stahl 2007 Germany	Journal article	Case series	Funduscopically and angiographically diagnosed RVO with central macular edema >250 µm (by OCT 3, fast macular thickness program) and duration >4 weeks; BCVA ≥0.1 (log Mar; decimal VA ≤0.8; fraction VA ≤20/25); age >18 years; patient able to give informed consent.	21	21	Single bevacizumab IVT injection 1.25 mg/0.05 mL. Re-injection after 9 weeks' follow-up was considered.	>2 months. Evaluations at baseline and 3, 6 and 9 weeks after injection.	visual acuity; adverse effects	Data also tabulated for individual patients. Subgroup analysis according to age of RVO and different occlusion types; latter only mentioned in the discussion section.

Key: BCVA best-corrected visual acuity; CRT central retinal thickness; ETDRS Early Treatment Diabetic Retinopathy Study; FA fluorescence angiography; IVT intravitreal; log MAR logarithm of the minimum angle of resolution; NR not reported; OCT optical coherence tomography; VA visual acuity.

3.3.3 Included Studies: Study Designs

3.3.3.1 How do the authors describe their studies?

The terminology used to describe study designs is open to interpretation by researchers and is often ambiguous. Many studies combine ideas from different basic designs, which make it difficult to classify them under one specific label. The descriptions of study design provided by the authors varied across the included reports, so the study design labels reported in Table 3.2 reflect those assigned by the authors. The 18 included studies are reported by their authors to be:

- four prospective studies (Costa 2007, Kondo 2009, Park 2009, Sivkova 2010)
- one prospective non-randomised study (Rensch 2009a)
- one prospective clinical trial/uncontrolled study (Funk 2009, Kriechbaum 2008, Kriechbaum 2009, Prager 2009)
- one non-randomised uncontrolled study (Rensch 2009b)
- nine case series/consecutive cases (Gutierrez 2008, Hung 2010, Jaissle 2009, Kreutzer 2008, Pai 2007, Pournaras 2008, Priglinger 2007, Stahl 2007, Yamashiro 2010)
- two studies of unspecified design (Hoeh 2009, Moschos 2008).

However, the study designs as reported by their authors are not entirely clear.

3.3.3.2 Comparative studies

Within the selected studies there were no 'true' comparative studies. Although Funk (Funk 2009) and Park (Park 2009) both described control groups within their studies, the control participants only provided reference samples for analysis and were not monitored for clinical effects such as visual function. Thus, no controlled studies were identified in this review.

3.3.3.3 Non-comparative studies

The methods described in the papers suggest that the nine non-case series studies (12 reports) are before-and-after studies with multiple measurements taken after the intervention (Costa 2007, Funk 2009, Hoeh 2009, Kondo 2009, Kriechbaum 2008, Kriechbaum 2009, Moschos 2008, Park 2009, Prager 2009, Rensch 2009a, Rensch 2009b, Sivkova 2010). Based on our definitions of study design, the included studies therefore comprise nine before-and-after studies and nine case series.

3.3.4 Included Studies: Interventions

In the included studies, bevacizumab was administered as an IVT injection, typically at a dose of 1.25 mg/0.05 mL. None of the studies evaluated bevacizumab in conjunction with other treatments such as triamcinolone acetonide and scatter laser photocoagulation, although one study (Kondo 2009) did report the use of peripheral scatter coagulation to prevent the development of retinal neovascularisation and vitreous hemorrhage, but only

when the eye showed a nonperfusion area of ≥10 disk diameters by fluorescein angiography. The majority of studies (12 studies, 67%) evaluated single injections, with some reporting reinjections for patients meeting specific retreatment criteria; others studied two or three injections given at 6-week intervals (Funk 2009, Kriechbaum 2008, Kriechbaum 2009, Kreutzer 2008, Prager 2009, Priglinger 2007, Rensch 2009a, Rensch 2009b, Sivkova 2010). Where reported, criteria for reinjection included the persistence or recurrence of macular edema (Costa 2007, Gutierrez 2008, Hoeh 2009, Jaissle 2009, Kondo 2009, Kriechbaum 2008, Pournaras 2008), treatment success, ineffectiveness or toxicity, defined variously (Kondo 2009, Kreutzer 2008, Priglinger 2007), loss of vision (Funk 2009, Hung 2008, Kriechbaum 2009, Pournouras 2008), and changes in retinal thickness (Hung 2008, Kriechbaum 2009, Pournouras 2008, Prager 2009, Stahl 2007). Table 3.3 provides further details of retreatment criteria and subsequent administration of bevacizumab.

Table 3.3: Retreatment following initial treatment with bevacizumab as reported in the included studies.

Author Year Country	Total patients (eyes)	Initial intervention	Retreatment criteria	Retreatment
BRVO alone				
Gutierrez 2008 Spain	12 (12)	Bevacizumab IVT injection (1.25 mg/0.5 mL) at baseline.	OCT indicates macular swelling (quantitatively characterized by a macular thickness >250 µm in any of the six radial scans).	Every 4 weeks. Four patients (33%) were retreated: 2 patients received two consecutive bevacizumab IVT injections and 2 patients received three injections.
Jaissle 2009 Germany	26 (26)	Bevacizumab IVT injection 1.25 mg/0.05 mL.	Existence of macular edema on OCT in the foveal area and VA 20/32 or worse.	Re-injection was considered at each follow-up visit and performed after informed consent of the patient. Mean of 2.4 re-injections (SD=NR range: 0–5) given during the 1-year follow-up. Mean of 1.6 re-injections for first 6 months (weeks 6 to 24) and a further 0.8 re-injections for latter 6 months (weeks 30 to 48).
Kondo 2009 Japan	50 (50)	Single bevacizumab IVT injection 1.25 mg/0.05 mL.	Recurrence of macular edema or initial injection not considered a success. Patient approval also required. Recurrence of macular edema was defined as a worsening of logMAR ≥0.2 after an initial improvement or an increase of foveal thickness ≥30% after the initial decrease. Treatment success was defined as at least one of the following: improvement in VA; logMAR ≥ -0.2; VA ≥0.7 (20/29, Snellen equivalent); decrease of foveal thickness ≥30%; or foveal thickness ≤230 µm.	Patients received, on average, 2 injections/eye (SD=NR; range: 1–4). After the initial injection, 33 eyes (66%) received a second injection at a mean interval of 15.9 weeks (SD=NR; range: 8–42), 11 eyes (22%) had a third injection at a mean of 18.2 weeks (SD=NR; range: 11–27), and 3 eyes (6%) had a fourth injection at a mean of 11.3 weeks (SD=NR; range: 10–13).
Kreutzer 2008 Germany	34 (34)	Bevacizumab IVT injections (1.25 mg/0.05 mL) on day 1 and 4 weeks thereafter. Only one eye was selected as the study eye.	Retreatment based on treatment success, ineffectiveness or toxicity, as determined by evaluation of VA and OCT findings. Treatment success was defined as: BCVA of study eye ≥79 letters (approximate Snellen equivalent of ≥20/30); average retinal thickness in the OCT central subfield ≤225 µm.	Retreatment given after 2nd injection. A mean of 2.9 IVT injections (SD=NR) were given during the study period. 15 (44%) eyes received two injections, 10 (29%) eyes three injections, 6 (18%) eyes four injections, 2 (6%) eyes five injections, and one (3%) eye six injections.

Author Year Country	Total patients (eyes)	Initial intervention	Retreatment criteria	Retreatment
			Treatment ineffectiveness (borderline improvement) was defined as: a decrease in mean retinal thickening of the study eye of ≥50 µm; an increase in BCVA ≥5 letters.	
Park 2009 South Korea	40 (40)	Bevacizumab IVT injection 1.25 mg/0.05 mL.	NR	NR
Rensch 2009a Germany	21 (21)	3 bevacizumab IVT injections (1.5 mg) at 6-week intervals.	NR	NR
Yamashiro 2010 Japan	15 of whom 3 had BRVO (19 of which 3 were eyes with BRVO)	Bevacizumab IVT injection (1.25 mg/0.05 mL) from a single batch.	NR	NR
CRVO alone				
Moschos 2008 Greece	10 (10)	0.2 mL IVT injection of bevacizumab 1.25 mg/0.05 mL.	NR	NR
Pournaras 2008 Switzerland	8 (8)	Bevacizumab IVT injection 1.25 mg/0.05 mL.	Decrease in BCVA, persistence of macular edema on angiograms or increase of central foveal thickness in comparison with the previous examination.	Re-injection considered at monthly assessment. 6 patients (75%) needed >1 injection. The 2nd injection was necessary at month 2 in 4 patients and at month 3 in 2 patients.
Priglinger 2007 Germany	46 (46).	Bevacizumab IVT injections (1.25 mg/0.05 mL) on day 1 and 4 weeks thereafter	Retreatment based on treatment success, futility or toxicity, as determined by evaluation of VA and OCT findings. Treatment success was defined as: BCVA of study eye ≥79 letters (approximate Snellen equivalent of ≥20/30); average retinal thickness in the OCT central subfield ≤225 µm. Treatment futility (borderline improvement) was defined as: a decrease in mean retinal thickness of the study eye of ≥50 µm (representing >20% reduction of calculated average retinal thickness); an increase in BCVA ≥5 letters.	Retreatment given after 2nd injection. Of 46 eyes, 14 (30%) received two consecutive monthly injections of IVT bevacizumab, 20 (43%) had three injections, and 12 (26%) received four injections. In all cases, treatment was discontinued due to treatment futility.
Rensch	25 (25)	3 bevacizumab IVT	NR	NR

Author Year Country	Total patients (eyes)	Initial intervention	Retreatment criteria	Retreatment
2009b Germany		injections (1.5 mg) given at 6-week intervals.		
Mixed/other RVO				
Costa 2007 Brazil	7 (7)	One IVT injection of 2.0 mg (0.08 mL) of bevacizumab at baseline.	Recurrence of macular edema, as documented by OCT.	Repeat IVT injection of 2.0 mg (0.08 mL) of bevacizumab at 12-week intervals.
EUDRACT (Funk 2009; Kriechbaum 2008; Kriechbaum 2009; Prager 2009) Austria	28 (29)	3 bevacizumab IVT injections (1.25 mg) at 4-week intervals (baseline and months 1 and 2).	Further treatment based on morphologic (OCT) and functional BCVA findings: OCT-documented persistent or recurrent edema with CRT (Stratus OCT) greater than a 250-µm threshold, or a 5-letter loss of vision on the ETDRS chart that was associated with recurrent edema. Otherwise, treatment withheld until the follow-up examination revealed an increase in CRT of ≥100 µm or loss in vision of ≥5letters (ETDRS) that was associated with recurrent edema, compared with the prior visit. If retinal thickness did not fall below the 250- µm threshold after 6 consecutive injections of 1.25 mg/0.05 mL bevacizumab, the monthly dose was doubled to 2.5 mg (0.1 mL).	Retreatment at monthly control visits, starting from visit 3. 10 patients were treated at month 3. During the following months, retreatment was needed in 1-4 patients, except for month 6, when 7 patients received retreatment. 13 eyes were treated but it is unclear how many patients were actually treated and whether retreatment was needed in only patients treated at month 3. Following the three initial injections, patients received a mean of 2.3 injections (SD=NR) between months 2 and 6 based on OCT findings. During the 6-month follow-up period, each patient received a mean of 5.3 (SD=NR) out of seven possible injections. Including the visit at month 12, each eye received a mean of 8 (SD=NR) out of 13 possible injections. Six eyes (20.7%) required continuous treatment up to month 12. Four eyes (13.8%) received only three initial treatments and no further retreatment. The retreatment rate was the same in both the BRVO and CRVO groups: a mean of 8 injections (SD=NR).
Hoeh 2009 Germany	61 (61)	Bevacizumab IVT injection 2.5 mg/0.1 mL.	Increasing or persistent macular edema in at least one of the scans. Criterion was morphologically visible edema in terms of intra- or subretinal fluid.	The minimum interval between two injections was 6-8 weeks. BRVO patients (n=34) received an average of 4.9± 2.9 injections. CRVO patients CRVO (n=27) received an average of 4.1± 2.2 injections.

Author Year Country	Total patients (eyes)	Initial intervention	Retreatment criteria	Retreatment
			A re-injection was also given if macular edema decreased but was still present. Subgroup analysis BRVO Group 1: average of 2.0±2.1 injections. Group 2: average of 4.6±3.1 injections. Group 3: average of 6.5±1.7 injections. CRVO Group 1: average of 2.6±2.0 injections. Group 2: average of 5.1±2.4 injections. Group 3: average of 4.5±1.4 injections.	
Hung 2010 Taiwan	25 (25)	Bevacizumab IVT injection 2.5 mg/0.1 mL.	Any of the following changes, compared with previous month's findings, as observed by clinical evaluating doctors during follow-up period: VA loss of ≥2 lines Snellen chart with OCT evidence of fluid in the macula; an increase in CRT of ≥100 µm; evidence of persistent fluid on OCT 1 month after the previous injection.	Repeated injections were performed on an as-needed basis when patients had persistent or recurrent macular edema. 92% of patients (23 eyes) underwent repeated injections. Patients received an average of 2 injections (SD=NR; range: 1–3).
Pai 2007 India	21 (21)	Single bevacizumab IVT injection 1.25 mg/0.05 mL.	NR	NR
Sivkova 2010 Bulgaria	127 in total, 31 with RVO (138 eyes in total, 31 with RVO)	3 consecutive bevacizumab injections (1.25 mg/0.5 mL) given at 4-week intervals.	NR	NR
Stahl 2007 Germany	21 (21)	Single bevacizumab IVT injection 1.25 mg/0.05 mL. Re-injection after 9 weeks' follow-up was considered.	Re-injection depended on individual responses to treatment and OCT findings.	Re-injection was considered after 9 weeks' follow-up. Tabulated data show one patient (5%) with CRVO underwent two re-injections.

Key: BCVA best-corrected visual acuity; CRT central retinal thickness; ETDRS Early Treatment Diabetic Retinopathy Study; FA fluorescence angiography; IVT intravitreal; log MAR logarithm of the minimum angle of resolution; NR not reported; OCT optical coherence tomography; SD standard deviation; VA visual acuity.

3.3.5 Included Studies: Sample Sizes and Duration of Follow-Up

The included studies of RVO had small study populations, with sample sizes ranging from 7 patients (7 eyes) (Costa 2007) to 61 patients (61 eyes) (Hoeh 2009). Two studies evaluated mixed patient populations. Sivkova included 127 patients (138 eyes) with proliferative diabetic retinopathy, type 2 diabetes and RVO, of whom 31 patients (31 eyes) had RVO (Sivkova 2010). Yamashiro described 15 cases (19 eyes) presenting with various ocular diseases, of which three (3 eyes) had BRVO (Yamashiro 2010). Only six studies (8 reports) provided specific details of where the participants had been recruited, namely eye hospitals (Costa 2007, Kondo 2009), university ophthalmology departments or hospitals (Funk 2009, Gutierrez 2008, Kondo 2009, Kriechbaum 2008, Kriechbaum 2009, Park 2009) and a veterans' general hospital (Hung 2010).

The duration of follow-up ranged from at least 1 month (Yamashiro 2010) to 1 year (Jaissle 2009, Kondo 2009, EUDRACT), although it was not always specifically reported. For example, some studies reported mean follow-ups: 6.3 months (Rensch 2009a), 6.5 months (Hung 2010) and 11 months (Funk 2009). Two reports described the 6- and 12-months results of one study (Kriechbaum 2008, Kriechbaum 2009), while another presented the first 4 months' results of an ongoing study expected to last 1 year (Pournaras 2008).

3.3.6 Included Studies: Population

This section describes the age and gender, RVO and macular edema characteristics and other conditions prevalent in the populations studied, and any prior treatments the participants may have undergone. The wide variety of participant inclusion criteria applied by the different studies (Table 3.2) meant that the populations would be diverse; they were also described variably across the included studies. Table 3.4 presents a summary of the characteristics of the included participants.

3.3.6.1 Participant age and gender

All studies reported the mean or median age of the study sample. The mean age ranged from 58 years (Park 2009) to 74.7 years (Yamashiro 2010) overall and in studies evaluating only the BRVO subtype, from 64.2 years (Moschos 2008) to 68 years (Pournaras 2008) in studies evaluating only the CRVO subtype, and from 58.2 years in CRVO patients (Funk 2009) to 70.3 years in CRVO patients (Hoeh 2009) in studies evaluating mixed RVO populations. The majority of reports (16 of 21) also reported the age range of their participants; some ranges were wider than others but, overall, the combined ranges spanned 29 to 89 years.

Participant gender was reported in all but two of the included studies (Rensch 2009b, Yamashiro 2010). The proportion of male participants ranged from 32% (Kondo 2009) to 67.4% (Priglinger 2007) across the 16 studies which reported such details, and was higher in half of them (8 studies). Males comprised 32% (Kondo 2009) to 61.8% (Kreutzer 2008) of studies evaluating only the BRVO subtype, 50% (Pournaras 2008) to 67.4% (Priglinger 2007) of studies evaluating only the CRVO subtype, and 43.3% (Sivkova 2010) to 61.9%

(Stahl 2007) of studies evaluating mixed RVO populations. Five studies had an approximately equal composition of males and females overall (46-54% male).

3.3.6.2 RVO and macular edema characteristics

The populations in the included studies presented with RVO of varying type and severity:

- Seven studies included patients with BRVO (Gutierrez 2008, Jaissle 2009, Kondo 2009, Kreutzer 2008, Park 2009, Rensch 2009a, Yamashiro 2010)
- Four studies included patients with CRVO (Moschos 2008, Pournaras 2008, Priglinger 2007, Rensch 2009b)
- Seven studies (10 reports) included a mixture of patients: one study of patients with central and hemicentral RVO (Costa 2007) and six studies of patients with BRVO and CRVO (Funk 2009, Hoeh 2009, Hung 2010, Kriechbaum 2008, Kriechbaum 2009, Pai 2007, Prager 2009, Sivkova 2010, Stahl 2007).
- Where reported, studies described eyes as having non-ischemic BRVO (Gutierrez 2008, Rensch 2009a), BRVO and macular ischemia (32.5%) or ischemic vein occlusion (42.5%) (Park 2008), non-ischemic CRVO (Moschos 2008, Rensch 2009b), a mixture of ischemic and non-ischemic CRVO (Pournaras 2008, Priglinger 2007), ischemic (Costa 2007) and non-ischemic (Funk 2009, Kriechbaum 2008) mixed RVO types, perfused macular edema (Jaissle 2009), and significant macular edema without marked retinal ischemia (Rensch 2009b).

The majority of studies (15 of 18) specifically reported the mean or median duration of RVO or defined it within the study inclusion criteria. It ranged from an estimated 15-20 days after onset in a study of patients with only CRVO (Moschos 2008) to a mean of 16.3 months for a subgroup of patients with CRVO (Funk 2009). Two studies reported the mean duration of subjective symptoms prior to start of treatment: 4.2 days for CRVO patients (Rensch 2009b) and 9.2 days for BRVO patients (Rensch 2009a).

All studies reported some measure of baseline visual acuity, indicating various degrees of impaired vision. 10 studies specified levels of VA or BCVA within their inclusion criteria (Costa 2007, Funk 2009, Gutierrez 2008, Hung 2010, Jaissle 2009, Kondo 2009, Kriechbaum 2008, Park 2009, Pournaras 2008, Sivkova 2010, Stahl 2007).

Table 3.4: Characteristics of the participants in the included studies.

Author Year Country	Number (%) Male/Female	Mean age (years) ± SD (range)	Type of RVO	Duration of RVO	Ischemia	Macular edema	Baseline visual acuity Mean ± SD	Ocular disease and risk factors n (%)	Prior treatment n (%)
BRVO alone									
Gutierrez 2008 Spain	5/7 (41.7/58.3)	Median: 66 ±4.16 (57-79)	BRVO:	Median: 4 ±1.81 Months	Non-ischemic	NR	BCVA: log MAR 1.32 ±0.43	HP:4 patients (33.3%)	NR
Jaissle 2009 Germany	14/9 (60.9/39.1)	Median: 68 (45-80) (23 eyes)	BRVO	Median: 7.1 months (range: 3.0-16.6) (23 eyes)	NR	Perfused macular edema.	VA: log MAR Median 0.50	NR	NR
Kondo 2009 Japan	16/34 (32/68)	64.3 (45-85)	BRVO	Mean: 13.6 weeks (range: 2-48)	NR	NR	BCVA: log MAR 0.53 (SD=NR) (20/69, Snellen equivalent)	DM: 2 patients (4%), without diabetic nephropathy HC: 8 patients (16%) HT: 25 patients (50%)	None
Kreutzer 2008 Germany	21/13 (61.8/38.2)	69 (44-86)	BRVO	Mean: 40 weeks (range: 1-300)	NR	Centre-involving retinal edema.	VA: log MAR 0.79 ±0.39	NR	14 eyes (41%) pretreated, 20 eyes (59%) not pretreated. 2 eyes (6%) received pars plana vitrectomy. 11 eyes (32%) received laser photocoagulation for macular edema (3 eyes also had IVT triamcinolone). One patient (3%) received IVT triamcinolone alone.
Park 2009 South Korea	14/26 (35.0/65.0) Responders: 8/16 (33.3/66.7) Non-	58 (37-74) Responder: 59 ± 11 Non-responder:	BRVO	Not specifically reported; inclusion criteria specify <=1 month Responders:	13 eyes (32.5%) with macular ischemia: 3 responders, 10 non-responders.	Clinically detectable macular edema involving the fovea.	BCVA: Snellen (log MAR) Responders: 0.81 ± 0.35 Non-responders: 0.76 ± 0.24	No patients with rubeosis iridis or ocular morbidity such as uveitis or vitreoretinal diseases. DM: No patients	No prior treatments for macular edema associated with BRVO.

Author Year Country	Number (%) Male/Female	Mean age (years) ± SD (range)	Type of RVO	Duration of RVO	Ischemia	Macular edema	Baseline visual acuity Mean ± SD	Ocular disease and risk factors n (%)	Prior treatment n (%)
	responders: 6/10 (37.5/62.5)	57 ± 11		mean 2.3 ± 1.4 weeks Non-responders: mean 1.9 ± 1.0 weeks	17 eyes (42.5%) with ischemic vein occlusion: 5 responders, 12 non-responders.			GLA: No patients HP: 15 responders (eyes), 10 non-responders (eyes); 26 patients receiving medication of hypertension.	
Rensch 2009a Germany	8/13 (38.1/61.9)	67.7 ±7.5 (range: NR)	BRVO	Mean duration of subjective symptoms prior to start of treatment 9.2 ± 5.4 days.	Non-ischemic	Significant macular edema (significant not defined).	VA: log MAR 0.81 ±0.53 (Snellen acuity 0.26 ± 0.23)	NR	None
Yamashiro 2010 Japan	NR	74.7 (68-79) (3 patients)	BRVO	NR	NR	NR	VA: log MAR - 0.16, 0.30 and 1.00 for 3 patients with BRVO	1/3 patients had cataracts. None of the patients had a history of uveitis.	IVT bevacizumab: 2/3 patients
CRVO alone									
Moschos 2008 Greece	6/4 (60/40)	64.2 (39-79)	CRVO	Estimated: 15-20 days after onset.	Non-ischemic	NR	BCVA: Snellen (log MAR) 0.115 ± 0.1 (1.01 ± 0.26)	None of the patients had ocular diseases, such as high myopia, central, or diffuse retinal degeneration that might influence multifocal electroretinography.	None of the patients had received any form of anti-vascular endothelial growth factor or IVT triamcinolone.
Pournaras 2008 Switzerland	4/4 (50.0/50.0)	68 (50-82)	CRVO	98 days (range: 3-289)	Ischemic: 2 Non-ischemic: 6	NR	BCVA: log MAR 0.84(SD=NR)	NR	NR
Priglinger	31/15	63.7	CRVO	29.3 weeks	Ischemic:	NR	BCVA:	NR	16 eyes (35%) had not

Author Year Country	Number (%) Male/Female	Mean age (years) ± SD (range)	Type of RVO	Duration of RVO	Ischemia	Macular edema	Baseline visual acuity Mean ± SD	Ocular disease and risk factors n (%)	Prior treatment n (%)
2007 Germany	(67.4/32.6)	(35-89)		(range: 1-150)	16 Non-ischemic: 30		log MAR 1.12 ± 0.44 ETDRS letters 34.5 ±22.2		received prior treatment. 20 eyes (43%) had received IVT triamcinolone; 5 of these also received radial optic neurotomy and 8 had panretinal laser photocoagulation. 2 eyes (4%) underwent radial optic neurotomy. 2 eyes (4%) underwent panretinal laser photocoagulation. Six patients (13%) had received hemodilution and/or high-dose intravenous glucocorticoids.
Rensch 2009b Germany	NR	67.7 ±7.5 (range: NR)	CRVO	Mean duration of subjective symptoms prior to start of treatment 4.2 ± 3.6 days.	Non-ischemic	Significant cystoid macular edema without marked retinal ischemia, as defined by the Central Retinal Vein Occlusion Study Group (1997).	VA: log MAR 0.97 ±0.40 (Snellen acuity 0.15 ± 0.13)	NR	None
Mixed/other RVO									
Costa 2007 Brazil	4/3 (57.1/42.9)	Median 65 (58-74)	Central: 5 Hemicentral: 2	Median 7 months (range 2.5-16)	Ischemic	NR	BCVA: log MAR (Snellen equivalent)	GLA: 5 patients HT: 5 patients	NR

Author Year Country	Number (%) Male/Female	Mean age (years) ± SD (range)	Type of RVO	Duration of RVO	Ischemia	Macular edema	Baseline visual acuity Mean ± SD	Ocular disease and risk factors n (%)	Prior treatment n (%)
							1.21 ± 0.36 (20/320)		
EUDRACT (Funk 2009; Kriechbaum 2008; Kriechbaum 2009; Prager 2009) Austria	13/15 (46.4/53.6)	BRVO: 62.5 ± 7.9 (range: NR) CRVO: 58.2 ± 11.5 (range: NR)	BRVO: 21 eyes (1 patient had BRVO in both eyes) CRVO: 8 eyes	BRVO: mean 10.4 ± 15.5 months CRVO: mean 16.3 ± 21.7 months	Non-ischemic	Clinically significant cystoid macular edema of >=250 µm, involving the foveal centre.	BCVA: log MAR BRVO: 0.48 ± 0.25 CRVO: 0.97 ± 0.55 BCVA: letters (Snellen equivalent) 50 (SD=NR) (20/100) BRVO: 55 (SD=NR) (20/80) CRVO: 35 (SD=NR) (20/200)	DM: No patients GLA: No study eye	None had received IVT triamcinolone. Laser coagulation: 4 BRVO, 0 CRVO
Hoeh 2009 Germany	33/28 (54/46) BRVO: 17/17 (50/50) CRVO:16/11 (59/41)	BRVO: 66.5±12.3 (range: NR) CRVO: 70.3±8.0 (range: NR)	BRVO: 34 CRVO: 27	BRVO: mean 37±77 weeks CRVO: mean 12±10 weeks	NR	Macular edema involving the foveal centre.	BCVA: lines/log MAR BRVO: 0.32 (0.50 ±0.29) CRVO: 0.18 (0.75 ±0.38)	NR	All patients naïve to treatment of macular edema. No previous vitreoretinal surgery, IVT injections or laser treatment had been performed.
Hung 2010 Taiwan	12/13 (48.0/52.0)	66.52 ± 13.75 (32-87) BRVO:	BRVO: 12 CRVO:13	NR	NR	NR	BCVA: Snellen (log MAR) 20/125 (1.09 ± 0.63)	CAD: 1 BRVO, 4 CRVO CVD: 0 BRVO, 1 CRVO	IVT steroids: 2 BRVO, 0 CRVO Laser: 4 BRVO, 2 CRVO

Author Year Country	Number (%) Male/Female	Mean age (years) ± SD (range)	Type of RVO	Duration of RVO	Ischemia	Macular edema	Baseline visual acuity Mean ± SD	Ocular disease and risk factors n (%)	Prior treatment n (%)
		64 ± 12 (49-80) CRVO: 69 ± 15 (32-87)						DM: 3 BRVO, 2 CRVO GLA: 3 BRVO, 2 CRVO HT: 11 BRVO, 6 CRVO	
Pai 2007 India	11/10 (52.4/47.6)	66.7 ± 8.5 (42-78)	BRVO: 12 CRVO: 9	NR	NR	Cystoid macular edema.	BCVA:Snellen (log MAR) 20/381 (1.28 ± 0.55) BRVO: 20/333 (1.22 ± 0.58) CRVO: 20/468 (1.37 ±0.54)	Unclear DM: 3 or 5 HT: 14 or 16	No prior treatment for vein occlusion.
Sivkova 2010 Bulgaria	RVO group: 13/17 (43.3/56.7) Gender reported for 30 patients; should be 31	RVO group: 68 (51-79)	BRVO: 16 CRVO: 15	Maximum 1 month	NR	Central macular edema.	BCVA: measure unclear BRVO: 0.09 ± 0.45 CRVO: 0.02 ± 0.85	NR	NR
Stahl 2007 Germany	13/8 (61.9/38.1)	64 (29-82)	BRVO: 7 CRVO: 14	Mean 5.2 months (range: 1-14)	NR	Central macular edema.	VA: log MAR for individual patients BRVO: Range: 0.3-1 CRVO: Range: 0.1-1.3	Patients with ocular diseases other than cataracts and glaucoma were excluded.	NR

Key: BCVA best-corrected visual acuity; CAD coronary artery disease; CVD cerebrovascular disease; DM diabetes mellitus; ETDRS Early Treatment Diabetic Retinopathy Study; GLA glaucoma; HC hypercholesterolemia; HT hypertension; IVT intravitreal; log MAR logarithm of the minimum angle of resolution; NR not reported; SD standard deviation; VA visual acuity.

3.3.6.3 Other ocular diseases and risk factors

Little information on other ocular diseases and risk factors present in the patient populations was reported. There was low consistency in reporting and the extent and level of detail presented varied widely. Ten of the 21 included reports provided details on the presence or absence of other ocular diseases (e.g. cataracts, glaucoma) or risk factors (e.g. diabetes, hypercholesterolemia and hypertension). One study reported the presence of both coronary artery disease and cerebrovascular disease (Hung 2010), six reported patients with hypertension (Costa 2007, Gutierrez 2008, Hung 2010, Kondo 2009, Pai 2007, Park 2009), three reported patients with diabetes (Hung 2010, Kondo 2009, Pai 2007), one reported patients with glaucoma (Costa 2007) and one reported patients with, hypercholesterolemia (Kondo 2009). Two studies mentioned the absence of conditions in general: ocular diseases, such as high myopia, central, or diffuse retinal degeneration that might influence multifocal electroretinography (Moschos 2008), and ocular morbidity such as uveitis or vitreoretinal diseases (Park 2009). Some studies mentioned specific conditions as criteria for exclusion, for example diabetes mellitus and glaucoma (Funk 2009, Park 2009) and patients with ocular diseases other than cataracts and glaucoma (Stahl 2007). However, the exclusion criteria were often extensive and these should be referred to for more specific details, for instance, studies excluding cases of uncontrolled hypertension, other diseases that reduced VA, and thromboembolic events occurring within set periods of time.

3.3.6.4 Prior treatment

The inclusion and exclusion criteria within studies relating to prior treatment varied, with studies recruiting participants who had never undergone treatment, had not received prior treatment within specified periods before the current treatment, or had undergone specific treatments. Of the 18 studies:

- Eight did not report these criteria
- Six reported that patients had either not been pretreated (Kondo 2009, Rensch 2009a, Rensch 2009b) or had not been pretreated for macular edema or vein occlusion (Hoeh 2009, Pai 2007, Park 2009)
- Two reported that no patients had received IVT triamcinolone or anti-vascular endothelial growth factor (Funk 2009, Moschos 2008)
- Two reported pretreatment of some participants.

Prior treatment was described as follows:

- 8 eyes (32%) had received IVT steroids or laser (Hung 2010);
- 14 eyes (41%) received with pars plana vitrectomy, laser photocoagulation with/without IVT triamcinolone, or IVT triamcinolone alone (Kreutzer 2008);
- 4 eyes (14%) had received laser coagulation (Kriechbaum 2009);
- 30 eyes (65%) had received various combinations of IVT triamcinolone, radial optic neurotomy, panretinal laser photocoagulation, hemodilution and high-dose intravenous glucocorticoids (Priglinger 2007);
- 2 of 3 patients (67%) had received IVT bevacizumab (Yamashiro 2010).

There were no apparent trends in prior treatment according to RVO subtype.

3.3.7 Quality Assessment

A randomised controlled trial, when properly conducted, limits the risk of bias. Hence, this type of study design is generally considered to be the most appropriate for evaluating the effects of an intervention. Non-randomised studies are at more risk of bias, even if well conducted, and flaws in the design and conduct of the study may increase bias further. These factors, and the potential for poor reporting, make it difficult to assess the methodological quality and risk of bias consistently across studies. Particular concerns are differences between the participants in different intervention groups and the lack of a formal research protocol.

There was great variation and inconsistencies in the reporting of the included studies, and the quality of the evidence was not high. Table 3.5 shows how far the included studies met the quality criteria used in this review.

Some studies reported detailed methods which seemed contrary to the study design they specified, for example studies described by the authors as case series often appeared to be protocol driven (Hung 2010, Stahl 2007), while in other studies the methods were unclear or insufficient detail was presented to follow the study direction (Funk 2009, Park 2009). The reporting of the participants' baseline characteristics was variable and often sparse, in particular for risk factors such as hypertension and diabetes. The outcome data were often lacking important detail (e.g. distance at which the VA test conducted) or were unclear (e.g. VA/BCVA measure used). Such factors hinder the interpretation of the results.

The included studies comprised 9 case series (Gutierrez 2008, Hung 2010, Jaissle 2009, Kreutzer 2008, Pai 2007, Pournaras 2008, Priglinger 2007, Stahl 2007, Yamashiro 2010) and what appeared to be nine before-and-after studies with multiple measurements (Costa 2007, Funk 2009, Hoeh 2009, Kondo 2009, Kriechbaum 2008, Kriechbaum 2009, Moschos 2008, Park 2009, Prager 2009, Rensch 2009a, Rensch 2009b, Sivkova 2010). The majority of studies (14/18) had explicit inclusion criteria, although these were not reported consistently for multiple reports of the EUDRACT study (Funk 2009, Kriechbaum 2008, Kriechbaum 2009, Prager 2009). The wide variation and sporadic reporting of the baseline characteristics of the participants meant that it was unclear whether the studies could be considered to be based on a representative sample from a relevant population; two studies that did not have a representative sample were those with mixed populations of patients with proliferative diabetic retinopathy, Type 2 diabetes and RVO (Sivkova 2010) and patients presenting with various ocular diseases (Yamashiro 2010). The lack of detail about the participants made it difficult to assess whether the participants were at a similar point in terms of disease progression; for example, study populations comprised various combinations of patients with BRVO, CRVO, hemicentral RVO and unspecified RVO type, as well as ischemic and non-ischemic states.

When deciding whether the duration of follow-up was long enough for important events to occur, we considered a 6-week follow-up as the minimum acceptable period and anything less than that to be unclear. Where applicable, all studies had sufficient follow-up to capture

short-term adverse effects arising from bevacizumab administration with the majority reporting outcomes at six months or longer However, given the small sample sizes (3-61 patients with RVO), it is highly unlikely that rare adverse reactions would have been captured.

By virtue of the tests used to evaluate VA and ocular structural measures, all studies used objective and subjective criteria to assess the efficacy outcomes.

Where reported, the major study limitations, as described by the authors, were small sample sizes, no control group and limited follow-up.

Table 3.5: Quality assessment of included studies.

Author Year Country	Checklist components (Case series, CRD Report 4, 2001) (Yes / No / Unclear)						Authors' comments relating to quality issues and study limitations
	Is the study based on a representative sample selected from a relevant population?	Are the criteria for inclusion explicit?	Did all individuals enter the survey at a similar point in their disease progression?	Was follow-up long enough for important events to occur?	Were outcomes assessed using objective criteria or was blinding used?[4]	If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	
Costa 2007 Brazil	Unclear	Yes	No	Yes	Yes/No	Not applicable	Conclusions about efficacy cannot be made in the absence of a control group. Future studies should consider issues such as whether to group hemicentral and CRVO together, characterization of the ischemic forms of RVO, perfusion status of the macula, and duration of symptoms.
EUDRACT (Funk 2009; Kriechbaum 2009; Kriechbaum 2 008; Prager 2009) Austria	Unclear	Yes	No	Yes	Yes/No	Not applicable	The small sample size means significant differences in cytokine levels may have been missed, and observed significances represent tendencies and need to be confirmed in further studies. Small number of patients in the CRVO group.
Gutierrez 2008 Spain	Unclear	Yes	No	Yes	Yes/No	Not applicable	No control group. Small sample size. Limited follow-up.
Hoeh 2009 Germany	Unclear	Yes	No	Yes	Yes/No	Unclear	Direct comparisons with the study are difficult because patients are categorized primarily by optical

[4] Yes/No denotes outcomes measured using objective (IOP, CRT etc.) and subjective (VA, BCVA) criteria.

Author Year Country	Checklist components (Case series, CRD Report 4, 2001) (Yes / No / Unclear)						Authors' comments relating to quality issues and study limitations
	Is the study based on a representative sample selected from a relevant population?	Are the criteria for inclusion explicit?	Did all individuals enter the survey at a similar point in their disease progression?	Was follow-up long enough for important events to occur?	Were outcomes assessed using objective criteria or was blinding used?[4]	If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	
							coherence tomography and not visual acuity.
Hung 2010 Taiwan	Unclear	Yes	No	Yes	Yes/No	Unclear	No control group of RVO without treatment. Relatively small number of patients. Short-term follow-up.
Jaissle 2009 Germany	Unclear	Yes	Unclear	Yes	Yes/No	Not applicable	None reported.
Kondo 2009 Japan	Unclear	Yes	Unclear	Yes	Yes/No	No	Lack of a control group. High withdrawal rate. Use of scattered laser photocoagulation in some patients might affect results because laser treatment can decrease vitreous levels of vascular endothelial growth factor.
Kreutzer 2008 Germany	Unclear	No	No	Yes	Yes/No	No	Lack of testing of functional visual acuity, such as use of reading tests.
Moschos 2008 Greece	Unclear	No	Unclear	Yes	Yes/No	Not applicable	Short-term results preclude an estimation of the long-term efficacy of IVT bevacizumab.
Pai 2007 India	Unclear	No	No	Yes	Yes/No	No	None reported.
Park 2009 South Korea	Unclear	Yes	No	Yes	Yes/No	Unclear	None reported.
Pournaras 2008	Unclear	Yes	No	Yes	Yes/No	Not applicable	Statistical analysis is limited given the restricted number of cases.

Author Year Country	Checklist components (Case series, CRD Report 4, 2001) (Yes / No / Unclear)						Authors' comments relating to quality issues and study limitations
	Is the study based on a representative sample selected from a relevant population?	Are the criteria for inclusion explicit?	Did all individuals enter the survey at a similar point in their disease progression?	Was follow-up long enough for important events to occur?	Were outcomes assessed using objective criteria or was blinding used?[4]	If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	
Switzerland							
Priglinger 2007 Germany	Unclear	No	No	Yes	Yes/No	No	Non-comparative study design.
Rensch 2009a Germany	Unclear	Yes	Yes	Yes	Yes/No	Not applicable	Non-randomisation. Relatively small number of patients enrolled. Insufficient follow-up to make a statement about the long-term effect of treatment.
Rensch 2009b Germany	Unclear	Yes	Yes	Yes	Yes/No	Not applicable	Lack of a control group. Uncontrolled trial. Relatively low number of enrolled patients; insufficient to allow a substantial statement about the safety of the treatment. Insufficient follow-up to make a statement about the long-term effect of the treatment. Study design precluded statements about the long-term effect of the therapy. Non-ischemic and ischemic types of CRVO have been defined in Central Retinal Vein Occlusion Study Group reports, but this classification is based on arbitrary angiographic findings and overlap between the two types is possible; given this, a certain level of retinal 'ischemia' may be present in all patients with this disease.

Author Year Country	Checklist components (Case series, CRD Report 4, 2001) (Yes / No / Unclear)						Authors' comments relating to quality issues and study limitations
	Is the study based on a representative sample selected from a relevant population?	Are the criteria for inclusion explicit?	Did all individuals enter the survey at a similar point in their disease progression?	Was follow-up long enough for important events to occur?	Were outcomes assessed using objective criteria or was blinding used?[4]	If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	
Sivkova 2010 Bulgaria	No	Yes	No	Yes	Yes/No	Not applicable	None reported.
Stahl 2007 Germany	Unclear	Yes	No	Yes	Yes/No	No	None reported.
Yamashiro 2010 Japan	No	Not applicable	Unclear	Not applicable	Yes/No	Not applicable	Not applicable

3.4 CLINICAL EFFECTS

All 18 studies reported some measure of clinical effects, but only 9 studies met the study design criteria for inclusion in this review (Costa 2007, Hoeh 2009, Kondo 2009, EUDRACT, Moschos 2008, Park 2009, Rensch 2009a, Rensch 2009b, Sivkova 2010). These were all uncontrolled studies with methodology suggestive of a before-and-after design with multiple measurements.

There were three studies of patients with only BRVO (Kondo 2009, Park 2009, Rensch 2009a), two studies of patients with only CRVO (Moschos 2008, Rensch 2009b) and four studies of patients with a mixture of BRVO, CRVO or hemicentral RVO (Costa 2007, Funk 2009, Hoeh 2009, Kriechbaum 2008, Kriechbaum 2009, Prager 2009, Sivkova 2010). Studies of mixed RVO populations presented the results overall and/or for subgroups of patients with BRVO and CRVO.

3.4.1 Branch RVO

Six studies evaluated clinical effects in patients with BRVO (Hoeh 2009, Kondo 2009, Kriechbaum 2008, Park 2009, Prager 2009, Rensch 2009a, Sivkova 2010). Of these, three studies had been conducted in mixed populations of patients with BRVO and CRVO (Hoeh 2009, Kriechbaum 2008, Prager 2009, Sivkova 2010). All six studies evaluated visual function and measures of ocular thickness. It should be noted that none of the studies evaluated contrast sensitivity which, although not specified in the inclusion criteria as a relevant outcome, may be of interest in this field.

3.4.1.1 Visual acuity

The studies used a mixture of tests to assess VA: Snellen charts (2 studies), the ETDRS (2 studies) and a standard Japanese decimal VA chart (1 study); one study did not report the VA test used (Sivkova 2010). The effects of treatment with bevacizumab were variable, ranging from significant improvements in VA to an initial significant response to treatment that stabilized over time. The findings are summarised in Table 3.6.

Three studies reported overall improvements in VA (Hoeh 2009, Kriechbaum 2008, Prager 2009, Rensch 2009a). In the Hoeh study (Hoeh 2009), patients with macular edema involving the foveal centre who were naïve to treatment for this condition showed a significant increase (1.8 lines) in BCVA at last visit (mean follow-up 59 weeks), as measured by ETDRS charts (lines and log MAR). Patients received an average of 4.9 injections, spaced at 6- to 8-week intervals. 38.3% of patients gained at least 3 lines in BCVA. The EUDRACT study reported 6- and 12-month results (Kriechbaum 2008, Prager 2009) for patients with non-ischemic BRVO and cystoid macular edema involving the foveal centre who had been treated with 3 consecutive bevacizumab injections at 4-week intervals. Significant increases in BCVA letters (ETDRS charts) compared with baseline were observed after 6 and 12 months (+18 letters); BCVA results were also expressed as Snellen equivalents. Significant improvements in VA (log MAR), measured using Snellen charts, were also observed throughout a 6-month study in patients with ‘significant’ (not defined), non-ischemic macular edema who had displayed subjective symptoms for less than 2 weeks

before the start of treatment (Rensch 2009a). Patients had received no prior treatment and were administered 3 bevacizumab injections at 6-week intervals.

Two studies reported a stable response to treatment following initial significant changes (Kondo 2009, Sivkova 2010). In a study of patients treated with 1-4 injections of bevacizumab, the mean BCVA (logMAR and Snellen equivalent), measured using a standard Japanese decimal VA chart did not change significantly after one month and had stabilised by 12 months. (Kondo 2009) Although 34 eyes (68%) showed gains of ≥0.2 log MAR in VA at 12 months, 5 eyes (10%) suffered a loss of ≥0.2 logMAR. Sivkova (Sivkova 2010) reported improvements of more than 3 lines in mean BCVA (measure unclear) compared to baseline after 6 weeks in patients with BRVO and central macular edema, within a mixed study sample of patients with proliferative diabetic retinopathy, type 2 diabetes and RVO. Patients received 3 consecutive bevacizumab injections at 4-week intervals and were followed for 16 weeks. The significant improvement observed at 6 weeks was stable up to 16 weeks (Sivkova 2010).

In their study of changes in VEGF and pigment epithelium-derived factor following an IVT injection of bevacizumab, Park et al. (Park 2009) compared log MAR BCVA (measured using Snellen chart) between responders and non-responders to treatment, none of whom had received prior treatment for macular edema associated with BRVO. A non-responder was defined as showing persistent macular edema at 6 weeks after injection, based on a <20% reduction of central macular thickness from baseline measurement and vision improvement by <0.3 logMAR. Although the initial log MAR was similar between the two groups, significant improvements were observed in responders compared with non-responders after 6 weeks. Hoeh (Hoeh 2009) also reported a subgroup analysis based on response to treatment, as judged by OCT. Group 1 comprised patients with dry OCT findings at last visit, and no recurrence of macular edema within the last 25 weeks; group 2 comprised patients had responded to treatment, with complete resolution of fluid at any follow-up visit, but whose macular edema had recurred within the last 25 weeks or at last visit; group 3 comprised all patients who had never shown a complete resolution of macular edema at any study visit. Patients received, on average, 2.0 (group 1), 4.6 (group 2) and 6.5 (group 3) injections at 6- to 8-week intervals, At the last visit, mean improvements in BCVA lines (ETDRS chart) were 1.6 lines in group 1 (significance not stated), 2.5 lines in group 2 (significance not stated) and 0.8 lines in group 3 (not significant). BCVA was 20/25 or better in 60% of group 1 and 20/40 or better in 50% of group 3, with no eyes worse than 20/200.

Where reported, the main factors correlated with improved vision were baseline VA (Hoeh 2009, Kondo 2009, and Kriechbaum 2008), patient age (Hoeh 2009, Kondo 2009) and CRT (Hoeh 2009, Rensch 2009a).

Table 3.6: Results for visual acuity: BRVO patients

Reference (author, year, country)	VA test	Distance	VA/BCVA reported: measure used	Visual acuity at baseline Mean +- SD	Visual acuity at follow-up Mean +- SD	Change (mean +-SD) or specified gain/loss in visual acuity (mean +- SD)	Overall
Hoeh 2009 Germany (N= 61patients; 61 eyes) (BRVO: 34 patients; 34 eyes) Subgroup analysis according to response Group 1: n=5 Group 2: n=17 Group 3: n=12	ETDRS chart ETDRS chart ETDRS chart	NR NR NR	BCVA: lines/log MAR (Unclear from results given). BCVA: lines BCVA: lines	0.32(0.50 logMAR±0.29)	Last visit: 0.48 (0.32 logMAR±0.21)	Last visit: 1.8±2.6 lines (p<0.001) Specified gain in VA >= 3 lines: 38.3% of patients at last visit. Last visit Group 1: 1.6±2.1 lines (significance not stated). Group 2:.5±2.3 lines (significance not stated). Group 3: 0.8±0.8 lines (not significant).	Bevacizumab resulted in a significant increase in VA at last visit. Final VA correlated significantly with initial VA, patient age and final central retinal thickness. 60.0% of the patients in group 1 had a BCVA of 20/25 or better. 50% of BRVO patients in group 3 had a VA of 20/40 or better, and no eyes were worse than 20/200.
Kondo 2009 Japan (N= 50 patients; 50 eyes)	Standard Japanese decimal VA chart Standard Japanese decimal VA chart	5 m 5 m	BCVA: log MAR BCVA: log MAR	0.53 (SD=NR) (20/69, Snellen equivalent)	1 month: 0.26(SD=NR) (20/37, Snellen equivalent) (significant improvement, p>0.0001 stated in text, but graph reports p<0.0001). 12 months: 0.26 (SD=NR) (20/37, Snellen equivalent)	Specified loss in VA >= 0.2 log MAR units: 5 eyes (10%) at 12 months. Specified gain in VA >= 0.2 log MAR units: 34 eyes (68%) at 12 months.	The mean log MAR did not change significantly after 1 month and had stabilized by 12 months. Factors correlated with better VA at 12 months were better baseline VA, younger patients and period from symptom onset.
EUDRACT (Kriechbaum 2008; Prager 2009) Austria (N= 28 patients; 29 eyes)	ETDRS charts	2 m	BCVA: letters (Snellen equivalent)	55 (SD=NR) (20/80)	6 months: 70 (SD=NR) (20/40) (significant improvement p<0.001) 12 months: 73 (SD=NR) ($20/32^{-2}$)	12 months: mean BCVA increased by +18 (p<0.001)	Statistically significant improvement in BCVA from baseline to 6 months and 12 months. Factors correlated with improved vision at 6 months were lower baseline BCVA, and time interval between

Reference (author, year, country)	VA test	Distance	VA/BCVA reported: measure used	Visual acuity at baseline Mean +- SD	Visual acuity at follow-up Mean +- SD	Change (mean +-SD) or specified gain/loss in visual acuity (mean +- SD)	Overall
(BRVO: 20 patients, 21 eyes)							onset of thrombosis and therapy initiation.
Park 2009 South Korea (N= 40 patients; 40 eyes) Subgroup analysis according to response Responders: n=24 Non-responders: n=16	Snellen chart	NR	BCVA: Snellen (log MAR)	Responders: 0.81 ± 0.35 Non-responders: 0.76 ± 0.24	6 weeks Responders: 0.31 ± 0.25 Non-responders: 0.65 ± 0.34		The initial log MAR BCVA was similar between responders and non-responders. BCVA was significantly improved in responders 6 weeks later compared with non-responders (p<0.001).
Rensch 2009a Germany (N= 21 patients; 21 eyes)	Snellen charts	NR	VA: log MAR	0.81 ±0.53 (Snellen acuity 0.26 ± 0.23)	1 month after 1st injection: 0.54 ±0.47 (p<0.001) 3 months: 0.55 ±0.46 (p=0.001) 6 months: 0.55 ±0.49 (p=0.002)		At all examinations during the follow-up of the study, VA was significantly higher than at baseline. Increase in VA correlated significantly with central retinal thickness.
Sivkova 2010 Bulgaria (N= 31 patients with RVO; 31 eyes with RVO) (BRVO: 16 patients; 16 eyes)	NR	NR	BCVA: measure unclear	0.09 ± 0.45	4 weeks: 0.3 ± 0.65 8 weeks: 0.4 ± 0.35 12 weeks: 0.4 ± 0.75 16 weeks: 0.4 ± 0.55		Mean BCVA improved by more than 3 lines compared to baseline at week 6 (p<0.001) and was stable up to 16 weeks.

Key: NR not reported; SD standard deviation.

3.4.1.2 Ocular imaging measurements

All six studies used OCT to measure either central retinal thickness (CRT), central macular thickness (CMT) or foveal thickness. The majority of studies reported significant reductions in macular thickness. The findings are summarised in Table 3.7.

Three studies evaluated CRT (Hoeh 2009, Kriechbaum 2008, Prager 2009, Rensch 2009a) in patients with 'significant' (not defined) macular edema or macular edema involving the foveal centre, who received multiple injections of bevacizumab. Hoeh (Hoeh 2009) observed significant reductions in CRT at the last visit (mean follow-up 59 weeks), while Rensch (Rensch 2009b) reported that CRT was significantly reduced compared with baseline at all examinations throughout the 6-month study. The highest increase in VA from 0.2 at baseline to 0.9 at 6 months after the first injection corresponded to a decrease in CRT from 635 µm at baseline to 204 µm. (Rensch 2009a) EUDRACT observed significant decreases in CRT at 6 months (Kriechbaum 2008) and 12 months (Prager 2009).

Two studies evaluated CMT (Park 2009, Sivkova 2010). Park (Park 2009) monitored CMT changes in responders and non-responders (defined in Section 3.4.1.1) to treatment with a single injection of bevacizumab in a study concerned primarily with the effect of bevacizumab on levels of VEGF. Although the initial CMT was similar between the two groups, significant reductions were observed in responders compared with non-responders after 6 weeks. Sivkova (Sivkova 2010) also reported changes in CMT in patients with BRVO and central macular edema given 3 consecutive bevacizumab injections at 4-week intervals and followed for 16 weeks. Decreases in CMT observed at 4 and 8 weeks (significance not stated) were stable up to 16 weeks, and patients with both high and low baseline CMT benefited from treatment.

The only study to evaluate foveal thickness (Kondo 2009) found mixed results in his 12-month study of patients treated with 1-4 injections of bevacizumab. There were significant reductions in foveal thickness at 1 and 3 months, but no significant changes after then. At 12 months, 29 eyes (50%) showed a decrease in foveal thickness of ≥30% and no eyes showed an increase in thickness of ≥30%. Nineteen eyes (38%) had a foveal thickness of <230 µm at 2 months; mean thickness at baseline was 523 µm.

Hoeh (Hoeh 2009) also reported a subgroup analysis based on response to treatment, as judged by OCT. The three groups of patients (defined as in Section 3.4.1.1) received multiple injections at 6- to 8-week intervals: mean numbers of injections administered were 2.0 (group 1), 4.6 (group 2) and 6.5 (group 3) injections. At the last visit, all three groups showed significant reductions in CRT from baseline values.

Table 3.7 Results for ocular imaging measurements: BRVO

Reference (author, year, country)	Imaging technique	Structural measure	Value at baseline Mean +/- SD (µm)	Value at follow-up Mean +/- SD (µm)	Overall
Hoeh 2009 Germany (N= 61patients; 61 eyes) (BRVO: 34 patients; 34 eyes) Subgroup analysis according to response Group 1: n=5 Group 2: n=17 Group 3: n=12	OCT OCT	CRT CRT	602 ±207 Group 1: 493 ±125 Group 2: 624 ±225 Group 3: 615 ±206	Last visit: 386 ±178 (p<0.001) Last visit Group 1: 217 ±46 (significant) Group 2: 382 ±155 (significant) Group 3: 463 ±200 (significant)	Bevacizumab treatment resulted in significant reduction of macular edema. Change in VA correlated with change in CRT. Subgroups: 15% of patients did not show a recurrence of macular edema for ≥25 weeks at last visit, 50% suffered recurrences within the last 25 wks, and 35% did not achieve complete resolution of macular edema at any follow-up visit after receiving a minimum of 3 injections.
Kondo 2009 Japan (N= 50 patients; 50 eyes)	OCT	Foveal thickness	523 (SD=NR)	1 month: 229 (SD=NR) (significant reduction, p<0.0001) 3 months: 300 (SD=NR) (significant increase) 12 months: 305 (SD=NR) Specified decrease in thickness >=30%: 29 eyes (58%) at 12 months. Specified increase in thickness >=30%: 0 eyes (0%) at 12 months.	The mean foveal thickness did not change significantly after 3 months. At 12 months, 19 eyes (38%) had foveal thickness of <230 µm.
EUDRACT (Kriechbaum 2008; Prager 2009) Austria (N= 28 patients; 29 eyes) (BRVO: 20 patients, 21 eyes) (BRVO at 12 months:	OCT	CRT	547(SD=NR)	6 months: 349 (SD=NR) (p<0.001) 12 months: mean CRT decreased by 241 (p<0.001)	Significant decrease in CRT was observed at 6 and 12 months.

Reference (author, year, country)	Imaging technique	Structural measure	Value at baseline Mean +/- SD (µm)	Value at follow-up Mean +/- SD (µm)	Overall
17 patients, 18 eyes)					
Park 2009 South Korea (N= 40 patients; 40 eyes) Subgroup analysis according to response Responders: n=24 Non-responders: n=16	OCT	CMT	Responders: 524 ± 116 Non-responders: 512 ± 95	6 weeks Responders: 265 ± 97 Non-responders: 427± 74	The initial CMT was similar between responders and non-responders CMT was significantly reduced in responders 6 weeks later compared with non-responders (p<0.001).
Rensch 2009a Germany (N= 21 patients; 21 eyes)	OCT	CRT	492 ±113	1 month after 1st injection: 294 ±117 (p<0.001) 3 months: 325 ±127 (p<0.001) 6 months: 316 ±117 (p<0.001)	At all examinations CRT was significantly reduced compared with baseline. The highest increase in VA from 0.2 at baseline to 0.9 at 6 months after the first injection corresponded to a decrease in CRT from 635 µm at baseline to 204 µm.
Sivkova 2010 Bulgaria (N= 31 patients with RVO; 31 eyes with RVO) (BRVO: 16 patients)	OCT	CMT	407 ±126	4 weeks: 301 ±147 8 weeks: 254 ±102 12 weeks: 242 ±94 16 weeks: 248 ±106	Changes in CMT were stable up to 16 weeks. Patients with low and high baseline CMT benefited from bevacizumab injections.

Key: CMT central macular thickness; CRT central retinal thickness; NR Not reported; OCT optical coherence tomography; SD standard deviation; VA visual acuity.

3.4.2 Central RVO patients

Five studies evaluated clinical effects in patients with CRVO (Hoeh 2009, Kriechbaum 2008, Moschos 2008, Prager 2009, Rensch 2009b, and Sivkova 2010). Of these, three studies had been conducted in mixed populations of patients with BRVO and CRVO (Hoeh 2009, Kriechbaum 2008, Prager 2009, and Sivkova 2010). All five studies evaluated visual function and measures of ocular thickness. It should be noted that none of the studies evaluated contrast sensitivity which, although not specified in the inclusion criteria as a relevant outcome, may be of interest in this field.

3.4.2.1 Visual acuity

The studies used a mixture of tests to assess VA: Snellen charts (2 studies) and the ETDRS (2 studies); one study did not report the VA test used (Sivkova 2010). The effects of treatment with bevacizumab were variable, ranging from significant improvements to fluctuations in VA. The findings are summarised in Table 3.8.

Two studies reported significant improvements in VA (Hoeh 2009, Rensch 2009b). At the last visit (61 weeks), a study of patients with macular edema involving the foveal centre who were naïve to treatment for this condition (Hoeh 2009) showed a significant increase in BCVA (1.9 lines), as measured by ETDRS charts (lines and log MAR). Patients received an average of 4.1 injections, spaced at 6- to 8-week intervals. 44.4% of patients gained at least 3 lines in BCVA. (Hoeh 2009) In a study by Rensch (Rensch 2009b), significant higher VA (log MAR) was observed at all follow-up examinations in a 6-month study of patients with significant cystoid macular edema without marked retinal ischemia (defined by the Central Retinal Vein Occlusion Study Group, 1997) who had displayed subjective symptoms for less than 1 week before the start of treatment. Patients had received no prior treatment and were administered 3 bevacizumab injections at 6-week intervals. At 6 months, 17 patients (68%) showed a gain in VA of 1 Snellen line, 17 patients (68%) showed a gain of 2 lines, and 14 patients (56%) showed a gain of 3 lines. Six patients (24%) did not show any improvement in VA at 1, 3 or 6 months after the first injection of bevacizumab, but a statistical subgroup analysis of these patients failed to detect any causes for this relatively poor outcome.

Two studies reported non-significant improvements in VA (Kriechbaum 2008, Moschos 2008, Prager 2009). Increases in BCVA (Snellen and log MAR) at 1 and 3 months were not significantly different from pre-treatment values for patients with recently diagnosed non-ischemic CRVO (estimated duration 15-20 days after onset) who had been treated with a single bevacizumab injection (Moschos 2008). The initial improvement in VA at 1 month had decreased by 3 months, although it still remained better than the pre-treatment value. EUDRACT reported 6- and 12-month results for patients with non-ischemic CRVO and cystoid macular edema involving the foveal centre who had been treated with 3 consecutive bevacizumab injections at 4-week intervals (Kriechbaum 2008, Prager 2009). Compared with baseline, improvements in BCVA letters (ETDRS charts) observed at 6 and 12 months were not statistically significant; some BCVA results were also expressed as Snellen equivalents.

Sivkova (Sivkova 2010) reported fluctuations, but not improvements, in BCVA (measure unclear) for a subgroup of patients with CRVO and central macular edema, within a mixed study sample of patients with proliferative diabetic retinopathy, type 2 diabetes and RVO. Patients received 3 consecutive bevacizumab injections at 4-week intervals and were followed for 16 weeks.

Hoeh (Hoeh 2009) also reported a subgroup analysis based on response to treatment, as judged by OCT. Group 1 comprised patients with dry OCT findings at last visit, and no recurrence of macular edema within the last 25 weeks; group 2 comprised patients had responded to treatment, with complete resolution of fluid at any follow-up visit, but whose macular edema had recurred within the last 25 weeks or at last visit; group 3 comprised all patients who had never shown a complete resolution of macular edema at any study visit. Patients received, on average, 2.6 (group 1), 5.1 (group 2) and 4.5 (group 3) injections at 6- to 8-week intervals, At the last visit, mean changes in BCVA lines (ETDRS chart) were +4.2 lines in group 1 (significance not stated), +1.5 lines in group 2 (significance not stated) and -0.4 lines in group 3 (not significant). BCVA was 20/25 or better in 44.4% of group 1 and 20/40 or better in 12.5% of group 3, with 37.5% of eyes worse than 20/200.

Two studies investigated factors affecting VA outcomes: one found a correlation between increased VA and decrease in macular thickness (Rensch 2009b), while the other found no correlation between improved BCVA and patient age, baseline VA, CRT, or duration of thrombosis.(Kriechbaum 2008).

Table 3.8: Results for visual acuity: CRVO patients

Reference (author, year, country)	VA test	Distance	VA/BCVA reported: measure used	Visual acuity at baseline Mean +- SD	Visual acuity at follow-up Mean +- SD	Change (mean +-SD) or specified gain/loss in visual acuity Mean +- SDEUDRACT	Overall
Hoeh 2009 Germany (N= 61 patients; 61 eyes) (CRVO: 27 patients; 27eyes) Subgroup analysis according to response Group 1: n=9 Group 2: n=10 Group 3: n=8	ETDRS chart ETDRS chart ETDRS chart	NR NR NR	BCVA: lines/log MAR (Unclear from results given). BCVA: lines BCVA: lines	0.18 (0.75 log MAR ±0.38)	Last visit: 0.27 (0.57 log MAR ±0.48)	Last visit: 1.9±3.2 lines (p<0.01) Specified gain in VA >= 3 lines: 44.4% of patients at last visit. Last visit Group 1: 4.2 ±2.6 lines (significance not stated). Group2: 1.5 ±3.3 lines (significance not stated). Group 3: −0.4 ±1.9 lines (not significant).	Bevacizumab treatment resulted in significant increase in VA at last visit. 44.4% of group 1 patients had a VA of 20/25 or better. 12.5% of patients in group 3 had a VA of 20/40 or better at last visit, and 37.5% were worse than 20/200.
EUDRACT (Kriechbaum 2008; Prager 2009) Austria (N= 28 patients; 29 eyes) (CRVO: 8 patients; 8 eyes) (CRVO at 12 months: 6 patients, 6 eyes)	ETDRS charts	2 m	BCVA: letters (Snellen equivalent)	35 (SD=NR) (20/200)	6 months: 47 (SD=NR) ($20/125^{-2}$) (improvement not statistically significant p>0.05)	12 months: mean BCVA increased by 7 letters (+1.5 lines) (p>0.05)	Improvement in BCVA from baseline to 6 months was not statistically significant. Change in BCVA at 12 months was not statistically significant. No correlation of BCVA outcome and age, baseline BCVA, baseline central retinal thickness, or duration of thrombosis.
Moschos 2008 Greece (N= 10 patients; 10 eyes)	Snellen chart	NR	BCVA: Snellen (log MAR)	0.115 ± 0.1 (1.01 ± 0.26)	1 month: 0.205 ± 0.1 (0.77 ± 0.3) 3 months: 0.165± 0.09 (0.84 ± 0.259)		There was a non-statistically significant improvement in mean VA 1 month after the bevacizumab injection. Three months later VA had decreased again, although it remained better than pre-

Reference (author, year, country)	VA test	Distance	VA/BCVA reported: measure used	Visual acuity at baseline Mean +- SD	Visual acuity at follow-up Mean +- SD	Change (mean +-SD) or specified gain/loss in visual acuity Mean +- SDEUDRACT	Overall
					No differences were statistically significant compared with pre-treatment values.		treatment values
Rensch 2009b Germany (N= 25 patients; 25 eyes)	Snellen charts Snellen charts	NR NR	VA: log MAR VA: lines	0.97 ±0.40 (Snellen acuity 0.15 ± 0.13)	1 month after 1st injection: 0.70 ±0.42 (p=0.007) 3 months: 0.69 ±0.46 (p=0.006) 6 months: 0.69 ±0.52 (p=0.015)	1 month after 1st injection: 95% CI of the difference: -0.47 to -0.08 3 months: 95: CI: -0.48 to -0.09 6 months: 95% CI: -0.50 to -0.06 Specified gain in VA. 1 month: +1 line, 17 patients (68%) +2 lines, 16 patients (64%) +3 lines 13 patients (52%) 3 months: +1 line, 16 patients (64%) +2 lines, 15 patients (60%) +3 lines 13 patients (52%) 6 months: +1 line, 17 patients (68%) +2 lines, 17 patients (68%) +3 lines 14 patients (56%)	At all examinations during the follow-up of the study, VA was significantly higher than at baseline. Increase in VA correlated significantly with decrease in macular thickness. Six (24%) of the 25 patients did not show an improvement in VA at 1, 3 or 6 months after the first injection of bevacizumab. The statistical sub-analysis of these patients failed to detect causes for the relatively poor outcome.
Sivkova 2010 Bulgaria (N= 31 patients with RVO; 31 eyes with RVO) (CRVO: 15 patients; 15 eyes)	NR	NR	BCVA: measure unclear	0.02 ± 0.85	4 weeks: 0.03 ± 0.65 8 weeks: 0.04 ± 0.45 12 weeks: 0.03 ± 0.25 16 weeks: 0.02 ± 0.75		VA fluctuated but did not improve.

Key: NR not reported; SD standard deviation.

3.4.2.2 Ocular Imaging Measurements

All five studies used OCT to measure either central retinal thickness (CRT), central macular thickness (CMT) or foveal thickness. The majority of studies reported significant reductions in macular thickness. The findings are summarised in Table 3.9.

Three studies evaluated CRT (Hoeh 2009, Kriechbaum 2008, Prager 2009, Rensch 2009b) in patients with cystoid macular edema and/or macular edema involving the foveal centre, who received multiple injections of bevacizumab. Hoeh (Hoeh 2009) observed significant reductions in CRT at the last visit (mean follow 61 weeks), while Rensch (Rensch 2009b) reported that CRT was significantly reduced compared with baseline at all examinations throughout the 6-month study. EUDRACT reported that the reduction in CRT at 6 months (96 µm) was not statistically significant, whereas the reduction at 12 months (-268 µm) was significantly different from baseline (Kriechbaum 2008, Prager 2009).

The only study to evaluate CMT (Sivkova 2010) reported a significant decrease in CMT at 4 weeks in patients with CRVO and central macular edema given 3 consecutive bevacizumab injections at 4-week intervals. The decrease was maintained for 16 weeks, and patients with both high and low baseline CMT benefited from treatment.

The only study to evaluate foveal thickness (Moschos 2008) reported statistically significant reductions compared with the pre-treatment value in a 3-month study of patients with recently diagnosed non-ischemic CRVO (estimated duration 15-20 days after onset) who had been treated with a single bevacizumab injection. There appear to be some discrepancies in the reporting and calculation of values in the original paper; we calculate that at 1 and 3 months, foveal thickness is approximately 43% lower than the pre-treatment value.

Hoeh (Hoeh 2009) also reported a subgroup analysis based on response to treatment, as judged by OCT. The three groups of patients (defined as in Section 3.4.2.1) received multiple injections at 6- to 8-week intervals: mean numbers of injections administered were 2.6 (group 1), 5.1 (group 2) and 4.5 (group 3) injections. At the last visit, all three groups showed significant reductions in CRT from baseline values.

Table 3.9: Results of ocular imaging measurements: CRVO patients

Reference (author, year, country)	Imaging technique	Structural measure	Value at baseline Mean +/- SD (µm)	Value at follow-up Mean +/- SD (µm)	Overall
Hoeh 2009 Germany (N= 61 patients; 61 eyes) (CRVO: 27 patients; 27eyes) Subgroup analysis according to response Group 1: n=9 Group 2: n=10 Group 3: n=8	OCT OCT	CRT CRT	748 ±265 Group 1: 590 ±270 Group 2: 771 ±213 Group 3: 878 ±268	Last visit: 373 ±224 (p<0.001) Last visit: Group 1: 248 ±69 (significant) Group 2: 278 ±132 (significant) Group 3: 633±222 (significant)	Bevacizumab treatment resulted in significant reduction of macular edema. Subgroups: 33% of patients did not show a recurrence of macular edema for ≥25 weeks at last visit, 37% suffered recurrences within the last 25 wks, and 30% did not achieve complete resolution of macular edema at any follow-up visit after receiving a minimum of 3 injections.
EUDRACT (Kriechbaum 2008‘ Prager 2009) Austria (N= 28 patients; 29 eyes) (CRVO: 8 patients; 8 eyes) (CRVO at 12 months: 6 patients, 6 eyes)	OCT	CRT	585 (SD=NR)	6 months: 489 (SD=NR) (p>0.05) 12 months: mean CRT decreased by 268 (p=0.007)	Reduction in CRT was not statistically significant at 6 months. Significant decrease in CRT was observed at 12 months. No correlation between BCVA and baseline CRT.
Moschos 2008 Greece (N= 10 patients; 10 eyes)	OCT	Foveal thickness	641.7 ±236.3	1 month: 364.6 ±120.0 3 months: 368.8 ±128.2 (367 in text)	Statistically significant reductions from the pre-treatment value (p<0.001). Authors stated that compared with pre-treatment values, foveal thickness was 43.7% lower at 1 month and 36.5% lower at 3 months. There appears to be some discrepancy in the calculation of these figures (should be around 43%) and values reported between the table and text. The author has yet to respond to an e-mail sent requesting further information and clarification.

Reference (author, year, country)	Imaging technique	Structural measure	Value at baseline Mean +/- SD (µm)	Value at follow-up Mean +/- SD (µm)	Overall
Rensch 2009b Germany (N= 25 patients; 25 eyes)	OCT	CRT	530 ±152	1 month after 1st injection: 347 ±127 (p<0.001) 95% CI of the difference: -231 to -133 3 months: 370 ±165 (p<0.001) 95% CI: -291 to -103 6 months: 346 ±129 (p<0.001) 95% CI: -240 to -130	At all examinations CRT was significantly reduced compared with baseline.
Sivkova 2010 Bulgaria (N= 31 patients with RVO; 31 eyes with RVO) (CRVO: 15 patients; 15 eyes)	OCT	CMT	617 ±214	4 weeks: 318 ±117 8 weeks: 294 ±128 12 weeks: 278 ±142 12 weeks: 306 ±114	CMT decreased significantly at week 4 (p<0.001) and was relatively stable up to the week 16. Patients with low as well as with high baseline CMT benefited from bevacizumab injections.

Key: BCVA best-corrected visual acuity, CMT central macular thickness; CRT central retinal thickness; NR not reported; OCT optical coherence tomography; SD standard deviation.

3.4.3 Mixed/Other RVO

Of the four studies (7 reports) describing mixed populations of patients with BRVO, CRVO or hemicentral RVO, only two evaluated the overall clinical effects in the mixed population (Costa 2007, Funk 2009, Kriechbaum 2008, Kriechbaum 2009, Prager 2009). Both studies evaluated visual function and measures of ocular thickness. None of the studies evaluated contrast sensitivity which, although not specified in the inclusion criteria as a relevant outcome, may be of interest in this field.

3.4.3.1 Visual acuity

Both studies reported improvements in VA (assessed using ETDRS or modified ETDRS charts) following treatment with bevacizumab. The findings are summarised in Table 3.10.

Costa (Costa 2007) reported that no patient showed a reduction in BCVA lines or log MAR (measured using the ETDRS or modified ETDRS charts) in a 25-week study of patients with ischemic central or hemicentral RVO who had not undergone prior treatment. Patients were initially given a single injection of bevacizumab, with further injections administered at 12-week intervals if macular edema recurred. The increase in BCVA was 3.34 lines at 12 weeks (n=7), 4.23 lines at 24 weeks (n=6) and 5.17 lines at 25 weeks (n=6), after the first injection. The proportion of patients achieving a specified gain in VA of ≥3 lines was 57.1% (4/7) at 12 week, and 66.7% (4/6) at 24 and 25 weeks. (Costa 2007)

EUDRACT investigated patients with non-ischemic BRVO/CRVO and clinically significant or cystoid macular edema involving the foveal centre who had been treated with 3 consecutive bevacizumab injections at 4-week intervals.(Funk 2009, Kriechbaum 2008, Kriechbaum 2009, Prager 2009). BCVA was monitored using ETDRS charts; results were presented as log MAR (Funk 2009), or ETDRS letters with Snellen equivalent.(Kriechbaum 2008, Kriechbaum 2009, Prager 2009). The study reports described significant improvements in BCVA from baseline to 12 months. Over 15 months (mean follow-up 11 months), Funk (Funk 2009) observed fluctuations in BCVA from baseline levels. The decrease in VEGF levels was associated with improved VA. Statistically significant improvements from baseline were found at 1, 3 and 6 months (Kriechbaum 2009) and 12 months (Kriechbaum 2008, Prager 2009). The overall gains reported were 5 letters (1 line) after 1 day and 15 letters (3 lines) at 6 months (Kriechbaum 2008), 15 letters (3 lines) at 6 months and 16 letters (3.2 lines) at 12 months (Prager 2009). A correlation was observed between improved BCVA and decreased CRT.

Table 3.10: Results for visual acuity: Mixed RVO

Reference (author, year, country) Type of RVO	VA test	Distance	VA/BCVA reported: measure used	Visual acuity at baseline Mean +- SD	Visual acuity at follow-up Mean +- SD	Change (mean +-SD) or specified gain/loss in visual acuity Mean +- SD	Overall
Costa 2007 Brazil (N= 7 patients; 7 eyes) Central + hemicentral RVO	modified ETDRS charts ETDRS modified ETDRS charts	NR NR NR	BCVA: lines BCVA: lines BCVA: log MAR (Snellen equivalent)	NR 1.21 ± 0.36 (20/320)	25 wks after 1st injection(1 wk after 3rd): 0.68 (SD=NR) (Snellen equivalent, 20/100+1)	n=7 1 wk after 1st injection: +2.37 6 wks:+3.97 12 wks: +3.34 n=6 13 wks after 1st injection (1 wk after 2nd): +4.70 18 wks: +5.07 24 wks: +4.23 n=6 25 wks after 1st injection (1 wk after 3rd): +5.17 Specified gain in VA >=3 lines 12 wks after 1st injection: 4 of 7 patients (57.1%) 24 wks: 4 of 6 patients (66.7%) 25 wks: 4 of 6 patients (66.7%)	No patient had a decrease in BCVA
EUDRACT							
Funk 2009 Austria (N= 13 eyes) BRVO + CRVO	ETDRS charts	2 m	BCVA: log MAR	All patients with RVO: 0.67 (value from graph; no SD). From text: BRVO: 0.48 ± 0.25 CRVO: 0.97 ± 0.55	VA fluctuated over the follow-up period. Selected results (below) are taken from the graph since not reported in the text (no SDs). 1 month: 0.42 3 months:0.35 6 months:0.37		Baseline values reported separately for BRVO and CRVO, but not follow-up data. The decrease in vascular endothelial growth factor levels was associated with an improvement in VA (p<0.001).

Reference (author, year, country) Type of RVO	VA test	Distance	VA/BCVA reported: measure used	Visual acuity at baseline Mean +- SD	Visual acuity at follow-up Mean +- SD	Change (mean +-SD) or specified gain/loss in visual acuity Mean +- SD	Overall
					9 months: 0.44 12 months: 0.25 15 months: 0.34		A positive association was observed between changes in CRT and VA (p<0.001).
Kriechbaum 2008 Austria (N= 28 patients; 29 eyes) BRVO + CRVO	ETDRS charts	2 m	BCVA: letters (Snellen equivalent)	50 (SD=NR) (20/100) Range: 3 – 78 letters (20/800 - 20/26^{-2})	1 day after 1st injection: 55 1 month: 60 (SD=NR) (20/63) (p<0.01) 3 months: 63 (SD=NR) (20/50-2) (p<0.01) 6 months: 65 (SD=NR) (20/50-2 (p<0.01)	1 day: change in mean BCVA 5 letters (1 line, p<0.01) 6 months: mean improvement 15 letters (SD=NR) (3 lines) (p<0.01)	Statistically significant improvements in BCVA from baseline were observed at 1, 3 and 6 months. Improved BCVA correlated with decrease in central retinal thickness.
Kriechbaum 2009 Austria (N= 7 patients; 7 eyes) BRVO + CRVO	ETDRS charts	2 m	BCVA: letters (Snellen equivalent)	51 ± 18 (20/100^{+1})	6 months: 65 ± 16 (20/50) 12 months: 66 ± 19 (20/50+1) (p<0.001)		At 12 months, there was a significant improvement in BCVA from baseline.
Prager 2009 Austria (N= 28 patients; 29 eyes) BRVO + CRVO	ETDRS charts	2 m	BCVA: letters (Snellen equivalent)	50 (SD=NR) (20/100) Range: 3 – 78 letters (20/800^{-2} - 20/26^{-2})	6 months: 65 (20/50) 9 months: 61 (20/64) 12 months: 66 (20/50^{+1}) Graph shows mean change in BCVA with standard errors.	6 months: +15 (p<0.001) 9 months: +11 (p<0.001) 12 months: +16 (p<0.001)	Results at 1 year showed that bevacizumab was associated with a significant improvement in VA (+3.2 lines; p<0.001).

Key: NR not reported; SD standard deviation.

3.4.3.2 Ocular imaging measurements

Two studies used OCT or spectral domain OCT to measure central retinal thickness (CRT), central macular thickness (CMT), central subfield thickness or mean retinal thickness. The findings were variable and are summarised in Table 3.11.

Costa (Costa 2007) reported data for individual patients with ischemic central or hemicentral RVO who had been treated with 1-3 injections of bevacizumab at 12-week intervals. The most favourable improvements in CMT were observed after 1 and 6 weeks, after which CMT increased compared with 6-week data. The most prominent changes in OCT examinations were observed after 6 and 18 weeks, which suggested that the maximum effect of bevacizumab may be achieved at least up to 6 weeks after injection.

EUDRACT reported mixed results. Over 15 months (mean follow-up 11 months) there were observed fluctuations in CRT from baseline levels (Funk 2009). The decrease in VEGF levels was associated with a decrease in CRT. Significant and stable decreases in CRT, centre subfield thickness and mean retinal thickness were reported over the 12-month follow-up; VA correlated with these parameters. (Kriechbaum 2009). Initial decreases in CRT were maintained up to 3 months, after which there was a non significant increase in CRT at 6 months following retreatment between months 3 and 6 (Kriechbaum 2008). A significant decrease in CRT (249 µm) was reported at 12 months (Prager 2009).

Table 3.11: Results for ocular imaging measurements: Mixed RVO patients

Reference (author, year, country) Type of RVO	Imaging technique	Structural measure	Value at baseline Mean +/- SD (µm)	Value at follow-up Mean +/- SD (µm)	Overall
Costa 2007 Brazil (N= 7 patients; 7 eyes) Central + hemicentral RVO	OCT	CMT	730.1 ± 257.4 Data also presented for individual patients (n=7): study eye, range: 411-1014 fellow eye, range: 163-246	Data presented for individual patients. n=7: wk 1, range: 149-564 wk 6, range: 165-496 wk 12, range: 167-677 n=6: wk 13, range: 152-480 wk 18, range: 166-491 wk 24, range: 189-580 wk 25, range: 152-435	The most favourable changes in macular architecture from baseline were observed at weeks 1 and 6 after each injection. By 12 weeks after each injection (i.e., weeks 12 and 24), CMT had increased compared with week 6 data for most patients. Changes in OCT examinations were most evident at wks 6 and 18, suggesting effects of bevacizumab may be maximal at least up to 6 wks after injection. Benefit persisted through last follow-up visit, but there was a clear tendency for macular edema to recur.
EUDRACT (4 reports)					
Funk 2009 Austria (N= 13 eyes) BRVO + CRVO	OCT	CRT	All patients with RVO: 553 (value from graph; no SD). From text: BRVO: 542.4 ± 192.7 CRVO: 572 ± 156.3	CRT fluctuated over the follow-up period. Selected results (below) are taken from the graph since not reported in the text. 1 month: 341 3 months: 326 6 months: 369 9 months: 455 12 months: 376 15 months: 387	The decrease in vascular endothelial growth factor levels was associated with a decrease in CRT ($p<0.001$). A positive association was observed between changes in CRT and VA ($p<0.001$).
Kriechbaum 2008 Austria (N= 28 patients; 29 eyes) BRVO + CRVO	OCT	CRT	558 (SD=NR) (range 353–928)	1 day after 1st injection: 401 (SD=NR) ($p<0.01$) 1 wk: 323 (SD=NR) ($p<0.01$) 1 month: 331 (SD=NR) ($p<0.01$) 3 months (1 month after 3rd injection): 328 (SD=NR) (range: 180-625) 6 months:	CRT remained stable at month 3. Retreatment between months 3 and 6 led to a slight, non significant increase in mean CRT at month 6. Improvement in BCVA correlated with decrease in CRT.

Reference (author, year, country) Type of RVO	Imaging technique	Structural measure	Value at baseline Mean +/- SD (µm)	Value at follow-up Mean +/- SD (µm)	Overall
				382 (SD=NR) (p<0.01) Mean change: 172 (SD=NR) (range: -579 to +111) (p<0.01)	
Kriechbaum 2009 Austria (N= 7 patients; 7 eyes) BRVO + CRVO	OCT OCT Spectral domain OCT	CRT CST MRT	562 ± 151 516 ± 113 334 ± 60	6 months: 384 ± 151 12 months: 315 ± 127 Both significant decreases from baseline (p<0.001) 6 months: 385± 127 12 months: 353 ± 112 (p<0.001) 6 months: 319± 36 (not significant) 12 months: 315 ± 35 (p<0.01)	The CRT, CST, and MRT decreased significantly and remained stable during the follow-up. VA correlated with OCT parameters (CRT, CST, MRT).
Prager 2009 Austria (N= 28 patients; 29 eyes) BRVO + CRVO	OCT	CRT	558 (SD=NR) (range: 353-928)	6 months: 382 Mean change: -176 (p<0.001) 9 months: 376 Mean change: -181 (p<0.001) 12 months: 309 Mean change: -249 (p<0.001) Graph shpws mean change in CRT with standard errors.	Results at 1 year showed that bevacizumab treatment was associated with a marked decrease in retinal thickness (-249 µm; p<0.001). Authors reported a slight increase (not significant) in CRT after 9 months in the text, but data show a slight decrease.

Key: CMT central macular thickness; CRT central retinal thickness; CST central subfield thickness; OCT optical coherence tomography; MRT mean retinal thickness; NR not reported; SD standard deviation; VA visual acuity.

3.5 ADVERSE EFFECTS

All but one study (Park 2009) considered adverse effects. Of the 17 studies (20 reports) that recorded such events, 8 were uncontrolled studies (Costa 2007, Funk 2009, Hoeh 2009, Kondo 2009, Kriechbaum 2008, Kriechbaum 2009, Moschos 2008, Prager 2009, Rensch 2009a, Rensch 2009b, and Sivkova 2010) and 9 were case series (Gutierrez 2008, Hung 2010, Jaissle 2009, Kreutzer 2008, Pai 2007, Pournaras 2008, Priglinger 2007, Stahl 2007, Yamashiro 2010). Adverse events were poorly reported across the included studies. In addition, the quality of the studies in terms of the adequacy of the methods used to capture adverse effects was low: the studies tended to lack formal protocols, and few studies defined adverse effects and how they would be reported. This suggests that the studies may underreport adverse effects. However, 14 studies did describe their intentions within the Methods section of their reports:

- Seven monitored specific adverse effects, sometimes as secondary outcomes (Funk 2009, Hung 2010, Kriechbaum 2008, Priglinger 2007, Sivkova 2010, Stahl 2007, Yamashiro 2010);
- Two monitored adverse effects in general (local and/or systemic) (Costa 2007, Gutierrez 2008);
- Five measured IOP but did not mention any assessment of adverse effects (Kreutzer 2008, Moschos 2008, Pai 2007, Rensch 2009a, and Rensch 2009b).

Only one of these 14 studies defined the targeted adverse effects (Priglinger 2007). The other studies did not describe any assessment of adverse effects in their methods (Hoeh 2009, Jaissle 2009, Kondo 2009, Pouraras 2008).

3.5.1 Ocular adverse effects

17 studies reported the presence or absence of ocular adverse reactions in general, or specific events such as raised IOP, endophthalmitis, retinal tears, retinal detachment, hemorrhage, hyperemia, inflammation, neovascular complications and cataract; some of these appear in the summary of product characteristics as serious adverse reactions. The data were sparse and the events were typically infrequent or absent. The findings are summarised in Table 3.12, arranged according to RVO subtype of the population for which the results were presented.

3.5.1.1 BRVO

Six studies described adverse effects in patients with BRVO (Gutierrez 2008, Jaissle 2009, Kondo 2009, Kreutzer 2008, Rensch 2009a, and Yamashiro 2010); the duration of follow-up ranged from at least 1 month to 1 year. One study described 14 cases of endophthalmitis in a mixed population of patients with various ocular diseases, although this was the purpose of the study (Yamashiro 2010). Three of these patients had BRVO. Conjunctive hyperemia and moderate inflammation were observed in 2 of the 3 eyes with endophthalmitis (Yamashiro 2010). In the remaining studies, where specifically reported, there were no cases of raised IOP or clinically significant cataract (Rensch 2009a), and no cases of

endophthalmitis, retinal detachment or neovascular complications (Jaissle 2009). All but one study (Yamashiro 2010) provided a statement regarding the absence of procedural- or drug-related complications, or ocular or local side effects.

3.5.1.2 CRVO

Four studies described adverse effects in patients with CRVO (Moschos 2008, Pournaras 2008, Priglinger 2007, and Rensch 2009b); the duration of follow-up ranged from 3 months to 1 year. Apart from one case (n=8) of localised hyperemia at the injection site which lasted less than one week (Pournaras 2008), where specifically reported, there were no cases of raised IOP (Moschos 2008), increased IOP or clinically significant cataract (Rensch 2009b), or endophthalmitis, retinal tears, lens trauma or rubeosis (Priglinger 2007). All four studies provided a statement regarding the absence of ocular or drug-related adverse effects. Priglinger (Priglinger 2007) also stated that no patient needed panretinal laser photocoagulation.

3.5.1.3 Mixed/other RVO

Seven studies (10 reports) described adverse effects in patients with mixed RVO: one in patients with central or hemicentral RVO (Costa 2007) and six in patients with BRVO or CRVO (Funk 2009, Hoeh 2009, Hung 2010, Kriechbaum 2008, Kriechbaum 2009, Pai 2007, Prager 2009, Sivkova 2010, Stahl 2007). The duration of follow-up ranged from 9 weeks to up to 15 months. Apart from 3 cases of conjunctival hyperemia and subconjunctival hemorrhage at the injection site in patients with central and hemicentral RVO (n=7) and no significant changes in IOP or lens status, reported by Costa (Costa 2007), studies reported the absence of adverse effects. No observations were recorded for the following events:

- Inflammation/uveitis (Costa 2007, Hung 2010, EUDRACT, Pai 2007);
- Retinal detachment (Hung 2010, EUDRACT, Pai 2007, Stahl 2007);
- Endophthalmitis (Hung 2010, EUDRACT, Pai 2007, Stahl 2007);
- Cataract (Pai 2007, EUDRACT, Stahl 2007);
- Increased IOP (Pai 2007, Stahl 2007);
- Neovascular complications (Hoeh 2009, EUDRACT);
- Central retinal occlusion (Stahl 2007);
- Glaucoma (Hung 2010);
- Retinal tears (Pai 2007);
- Vitreous hemorrhage (Hung 2010).

In the EUDRACT study, Funk (Funk 2009) stated that in a subgroup of 13 patients, none showed signs of converting into a non-perfusion type with ischemia-related complications under therapy, despite extremely low levels of VEGF. None of the 28 patients in EUDRACT showed signs of progression to ischemic BRVO or CRVO (Kriechbaum 2008) and no negative side effects were observed during the 1-year observation period (Kriechbaum 2009). In another study, Stahl (Stahl 2007) ruled out possible side effects of the injection at each follow-up visit. The other studies provided more general statements regarding the absence of drug- or injection-related side effects, ocular toxicity, and ocular or local adverse effects, short-tem or severe.

Table 3.12: Reported adverse effects: Ocular

Author Year Country Type of RVO	Length of follow-up	IOP	Endophthalmitis	Retinal tears or detachment	Hemorrhage	Hyperemia (red eye) or inflammation	Other	Overall
Gutierrez 2008 Spain (N= 12 patients; 12 eyes) BRVO	6 months							Authors stated that no ocular adverse events were observed.
Jaissle 2009 Germany (N= 26 patients; 26 eyes) BRVO	12 months		0 cases	Detachment: 0 cases			Neovascular complication: 0 cases	Authors stated that no other severe procedure-related complications were observed in a total of 78 injections. No obvious bevacizumab-related ocular adverse events were apparent. No patient needed peripheral sectoral laser photocoagulation during the follow-up.
Kondo 2009 Japan (N= 50 patients; 50 eyes) BRVO	12 months							Authors stated that no serious local bevacizumab-related adverse events were observed during the 12 months of this study.
Kreutzer 2008 Germany (N= 7 patients; 7 eyes) BRVO	6 months	NR (IOP was monitored)						Authors stated that no side effects of the IVT injection of bevacizumab were seen.
Rensch 2009a Germany (N= 21 patients; 21 eyes) BRVO	Mean 6.3 months	No increases observed.					Clinically significant cataract: 0 cases	Authors state that IVT application of bevacizumab was not associated with side-effects such as raised IOP or cataract progression during the follow-up.

Author Year Country Type of RVO	Length of follow-up	IOP	Endophthalmitis	Retinal tears or detachment	Hemorrhage	Hyperemia (red eye) or inflammation	Other	Overall
Yamashiro 2010 Japan (N=3 patients with BRVO; 3 eyes with BRVO) BRVO	Minimum 1 month		3 eyes			2 of 3 eyes conjunctive hyperemia 2 of 3 eyes moderate inflammation		
Moschos 2008 Greece (N= 10 patients; 10 eyes) CRVO	3 months	No cases of raised IOP.						Authors stated that no patient manifested ocular side effects or IOP increase.
Pournaras 2008 Switzerland (N= 8 patients; 8 eyes) CRVO	12 months					Localised hyperemia at injection site; lasted <1 week.		Authors stated that no serious adverse effects were observed.
Priglinger 2007 Germany (N= 46 patients; 46 eyes) CRVO	6 months		0 cases	Tears: 0 cases			Lens trauma: 0 cases. Rubeosis: 0 cases	Authors stated that no patient developed need of panretinal laser photocoagulation, and no case of an adverse event was found.
Rensch 2009b Germany (N= 25 patients; 25 eyes) CRVO	6 months	No increases observed.					Clinically significant cataract: 0 cases	Authors state that IVT application of bevacizumab was not associated with side-effects such as elevated IOP or a clinically detected increase in cataract during the follow-up.

Author Year Country Type of RVO	Length of follow-up	IOP	Endophthalmitis	Retinal tears or detachment	Hemorrhage	Hyperemia (red eye) or inflammation	Other	Overall
Costa 2007 Brazil (N= 7 patients; 7 eyes) Central and hemicentral	6 months	No significant changes.	No clinical evidence.		Conjunctival hyperemia & subconjunctival hemorrhage at injection site: 3 cases.	Conjunctival hyperemia & subconjunctival hemorrhage at injection site: 3 cases. No clinical evidence of inflammation.	No significant changes in lens status	No clinical evidence of other ocular toxicity. Authors stated that no serious drug-related adverse events were observed.
EUDRACT (Funk 2009; Kriechbaum 2008; Kriechbaum 2009; Prager 2009) Austria BRVO+CRVO (N= 28 patients; 29 eyes)	Up to15 months (mean 11 months)		6 months: 0 cases	6 months: Detachment: 0 cases		6 months: uveitis: 0 cases	Neovascular complications: NR (these were monitored)	None of the patients showed signs of conversion into a nonperfusion type with ischemia-related complications under therapy. Authors stated that none of the patients showed any severe local adverse events. None showed progression to ischemic BRVO or CRVO. Authors stated that no negative side effects occurred during the 1-year observation period.
Hoeh 2009 Germany (N= 61patients; 61 eyes) BRVO+CRVO	Minimum 6 months						Neovascular complications: 0 cases	Authors stated that no patient developed neovascularisation during therapy.
Hung 2010 Taiwan (N= 25 patients; 25 eyes) BRVO+CRVO	Mean 6.5 months (range: 5.5-12)		0 cases	Detachment: 0 cases	Vitreous: 0 cases	Uveitis: 0 cases	Glaucoma: 0 cases. Neovascular complications: monitored but NR	Authors stated that none of the patients showed any ocular adverse events.

Author Year Country Type of RVO	Length of follow-up	IOP	Endophthalmitis	Retinal tears or detachment	Hemorrhage	Hyperemia (red eye) or inflammation	Other	Overall
Pai 2007 India (N= 21 patients; 21 eyes) BRVO +CRVO	3 months	No increases observed.	0 cases	Tears: 0 cases Detachment: 0 cases		Inflammation: 0 cases	Cataract: 0 cases	At both 4 and 12 weeks, the authors stated that there were no serious ocular side effects.
Sivkova 2010 Bulgaria (N= 31 patients with RVO; 31 eyes with RVO) BRVO +CRVO	4 months							Authors stated that there were no significant side effects of IVT bevacizumab application during the follow-up period.
Stahl 2007 Germany (N= 21 patients; 21eyes) BRVO +CRVO	2 months	No rise observed.	0 cases	Detachment: 0 cases			Central retinal occlusion: 0 cases Cataract: 0 cases	Authors stated that on each follow-up visit, possible side effects of the injection were ruled out, and they did not observe any short-term adverse effects during their study.

3.5.2 Systemic Adverse Effects

Common adverse reactions associated with bevacizumab include, amongst others, arteriothrombolic events, gastrointestinal disorders, hypersensitivity reactions, hypertension, proteinuria, and blood and lymphatic system disorders. Thirteen of the 17 studies reported the presence or absence of systemic adverse reactions in general. The data were sparse and the events were absent. The findings are summarised in Table 3.13, arranged according to RVO subtype of the population for which the results were presented.

3.5.2.1 BRVO

Of the six studies reporting on patients with BRVO alone, four made statements concerning the lack of adverse effects in general (Gutierrez 2008, Jaissle 2009, Kondo 2009, Kreutzer 2008) and two made no mention of systemic adverse effects either in their methods or results (Rensch 2009a, Yamashiro 2010). No obvious or serious systemic adverse events (Gutierrez 2008, Jaissle 2009, and Kondo 2009) or injection-related side effects (Kreutzer 2008) were observed during the duration of the studies (6 months to 1 year).

3.5.2.2 CRVO

Four studies reported on patients with CRVO alone: three made statements concerning the lack of adverse effects in general (Moschos 2008, Pournaras 2008, Priglinger 2007), while the other neither described an assessment of systemic adverse effects nor reported any (Rensch 2009b). No patients showed clear systemic side effects (Moschos 2008) and no adverse effects (Priglinger 2007) or serious adverse effects (Pournaras 2008) were observed over 3-6 months' follow-up.

3.5.2.3 Mixed/other RVO

Of the seven studies (10 reports) of mixed populations of RVO, six commented upon adverse effects (Costa 2007, Funk 2009, Hung 2010, Kriechbaum 2008, Kriechbaum 2009, Pai 2007, Prager 2009, Sivkova 2010, Stahl 2007) and one neither described an assessment of adverse effects nor reported any adverse effects (Hoeh 2007).

In the only study of patients with central and hemicentral RVO, no significant changes in blood pressure were observed during the 25-week study (Costa 2007). The authors also stated that no serious-drug related adverse effects were seen.

The remaining five studies (8 reports) were of patients with BRVO and CRVO; the duration of follow-up ranged from 9 weeks to up to 15 months. Two studies (4 reports) reported no cases of thromboembolic events (Funk 2009, Hung 2010, Kriechbaum 2008, Prager 2009). No cases of systemic hypertension or kidney failure in the EUDRACT study were reported (Prager 2009), while Hung (Hung 2010) reported no cardiovascular accidents. Pai tested for retinal toxicity but did not report any results (Pai 2007), while Stahl ruled out possible side effects of the injection at each follow-up visit (Stahl 2007). Four studies provided statements concerning the absence of systemic adverse effects (Funk 2009, Hung 2010, Kriechbaum

2008, Pai 2007, Prager 2009) and two studies reported the absence of side effects in general (Sivkova 2010, Stahl 2007).

Table 3.13: Reported adverse effects: Systemic

Author Year Country	Length of follow-up	Event (e.g. death, headache, worse hypertension, nausea/vomiting, thromboembolic event)	Number (%) experiencing the event	Overall
Gutierrez 2008 Spain (N= 12 patients; 12 eyes) BRVO	6 months			Authors stated that no systemic adverse events were observed.
Jaissle 2009 Germany (N= 26 patients; 26 eyes) BRVO	12 months			Authors stated that no obvious bevacizumab-related systemic adverse events were apparent.
Kondo 2009 Japan (N= 50 patients; 50 eyes) BRVO	12 months			Authors stated that no serious systemic bevacizumab-related adverse events were observed during the 12 months of this study.
Kreutzer 2008 Germany (N= 7 patients; 7 eyes) BRVO	6 months			Authors stated that no side effects of the IVT injection of bevacizumab were seen.
Rensch 2009a Germany (N= 21 patients; 21 eyes) BRVO	Mean 6.3 months	NR	NR	NR
Yamashiro 2010 Japan (N= 3 patients with BRVO; 3 eyes with BRVO) BRVO	Minimum 1 month	NR	NR	NR
Moschos 2008 Greece (N= 10 patients; 10 eyes) CRVO	3 months			Authors stated that no patients manifested systemic side effects.
Pournaras 2008 Switzerland (N= 8 patients; 8 eyes) CRVO	12 months			Authors stated that no serious adverse effects were observed.

Author Year Country	Length of follow-up	Event (e.g. death, headache, worse hypertension, nausea/vomiting, thromboembolic event)	Number (%) experiencing the event	Overall
Priglinger 2007 Germany (N= 46 patients; 46 eyes) CRVO	6 months			Authors stated that no case of an adverse event was found.
Rensch 2009b Germany (N= 25 patients; 25 eyes) CRVO	6 months	NR	NR	NR
Costa 2007 Brazil (N= 7 patients; 7 eyes) Central and hemicentral	6 months	No significant changes in blood pressure.		Authors stated that no serious drug-related adverse events were observed.
EUDRACT (Funk 2009; Kriechbaum 2008; Kriechbaum 2009; Prager 2009) Austria (N= 28 patients; 29 eyes) BRVO +CRVO	Up to 15 months (mean 11 months)	Arterial thrombolic events Systemic hypertension Kidney failure	0 0 0	Authors stated that no severe systemic adverse effects had been observed at 6 or 12 months.
Hoeh 2009 Germany (N= 61patients; 61 eyes) BRVO +CRVO	6 months	NR	NR	NR
Hung 2010 Taiwan (N= 25 patients; 25 eyes) BRVO +CRVO	Mean 6.5 months (range: 5.5-12)	Cardiovascular accident Thromboembolic events	0 0	Authors stated that no systemic adverse events were noted.
Pai 2007 India (N= 21 patients; 21 eyes) BRVO +CRVO	3 months	Authors also tested for retinal toxicity; results not reported.		At both 4 and 12 weeks, the authors stated that there were no serious systemic side effects.
Sivkova 2010 Bulgaria (N= 31 patients with RVO; 31 eyes with RVO) BRVO +CRVO	4 months			Authors stated that there were no significant side effects of IVT bevacizumab application during the follow-up period.
Stahl 2007 Germany (N= 21 patients; 21eyes) BRVO +CRVO	2 months			Authors stated that on each follow-up visit, possible side effects of the injection were ruled out, and they did not observe any short-term adverse effects during their study.

3.6 HEALTH-RELATED QUALITY OF LIFE

No non-randomised studies were identified that assessed HRQoL. None of the studies eligible for the reviews of clinical effects and adverse effects reported HRQoL.

Section 4: Discussion and Recommendations

4.1 OVERVIEW

Within the UK, IVT bevacizumab is not approved across three dimensions: it does not have approval for any ocular indications; it is not presented in a licensed formulation for administration in the eye; and it does not have approval for compounding into smaller doses for ocular use. Few RCTs have been conducted and no large clinical trial programme is being conducted to support registration. This review aimed to assess evidence from non-randomised studies on the clinical effectiveness and safety of bevacizumab in the treatment of macular edema secondary to RVO, branch or central.

4.2 MAIN FINDINGS

A literature search had identified 64 potentially relevant records for inclusion in the current review. Following assessment, 21 reports (corresponding to 18 studies) provided evidence on the effect of bevacizumab in the treatment of adults with macular edema secondary to RVO, branch or central. These were non-comparative studies: in the two studies with controls, the control groups merely provided references samples for analysis and were not monitored for clinical effects, thus we did not consider them true controlled trials for the purpose of this review. All studies had been published from 2007 onwards.

Diverse study designs and wide variation and inconsistencies in reporting made it difficult to judge the reliability and generalisability of the included studies. Whilst poor reporting may not reflect the actual conduct of the original studies, it does hamper an assessment of their quality. The quality of the evidence presented is likely to be low given the inherent biases in non-randomised studies. The principal study designs, as described by the authors, were prospective studies, case series, non-randomised studies and a clinical trial; two studies were of an unspecified design. However, it is not uncommon for studies to combine features from several study designs and for researchers to classify studies differently, especially in the absence of standard definitions for some designs. Closer inspection of the methods described in the reports of the non-case series suggested that these were before-and-after studies with outcomes monitored pre-treatment and at multiple time points after the intervention. The before-after study design is a common approach to measure the effect of an intervention when it may not be practical or possible to obtain concurrent controls. However, this design is not without its limitations: it may be difficult to ascribe causality or draw inferences about the success of an intervention given such issues as the lack of a control group, the lack of control for confounders, the comparability of participants in the 'before' and 'after' group (change in circumstances or health), temporal trends in outcomes (changes over time regardless of whether an intervention has been applied), and the potential for focusing on participants in 'problem areas' (e.g. those with extreme conditions).

Thus, the inferences drawn from a before-and-after study should be cautious. (A primer on before–after studies: evaluating a report of a “successful” intervention 1999).

Study populations with RVO (BRVO, CRVO or hemicentral RVO) were generally small, ranging from 7 patients (7 eyes) to 61 patients (61 eyes). Calculations of sample size were not reported. Two studies evaluated mixed populations of patients with various ocular diseases, but the proportion of eyes with RVO was small: 22.5% (31/138 eyes) in one study and 15.8% (3/19 eyes) in the other. The duration of follow-up was short, ranging from at least 1 month to 1 year, although it was not always specifically reported; follow-up of approximately 6 months (26 weeks) or shorter seemed more prevalent. It is likely that follow-up was sufficient in most cases to capture any effects of bevacizumab. Bevacizumab was administered alone, either as single, sequential or repeat IVT injections (typically 1.25 mg/0.05 mL), with patients often having to satisfy specific conditions in order to receive retreatment. None of the studies evaluated bevacizumab in conjunction with other treatments for macular edema secondary to RVO, although one reported the concomitant use of peripheral scatter coagulation to prevent the development of retinal neovascularisation and vitreous hemorrhage.

The studies applied a variety of participant eligibility criteria, resulting in a broad spectrum of included participants; this variability in patient samples across the included studies precludes meta-analysis The baseline characteristics of the participants were inconsistently reported across studies and at varying levels of detail, which made it difficult to ascertain whether the study samples chosen reflected the population of patients with macular edema secondary to RVO. Only the age and gender of the participants were consistently reported. The patient population presented with RVO of varying type and severity. Some studies described the degree of ischemia and the underlying macular edema. Very few studies reported comprehensive details of other ocular diseases (e.g. cataracts, glaucoma) or underlying risk factors (e.g. diabetes, hypertension) for RVO.

The effects of treatment of BRVO with bevacizumab were variable, with studies reporting either a significant improvement in VA compared with baseline or an initial significant change that stabilized over the duration of follow-up (2-12 months). The majority of studies reported significant reductions in macular thickness from baseline. Two studies observed correlations between improved vision and central retinal thickness.

The effects of treatment with bevacizumab for CRVO were also variable, with studies reporting either significant improvements or fluctuations in VA and the majority of studies reported significant reductions in macular thickness from baseline up to 12 months’ follow-up. One of the two studies investigating factors affecting VA outcomes found a correlation between improved VA and decrease in macular thickness, while the other study found no such correlation. Only two studies reported overall data for mixed populations of patients with BRVO or CRVO, and central or hemicentral RVO. Both studies reported improvements in VA following treatment with bevacizumab. However, their findings in relation to macular thickness were variable: one study reported a short-term benefit while the other, which was published as four separate articles describing different aspects, reported mixed results.

The majority of studies reported on adverse events but did not appear to have conducted a comprehensive assessment of adverse events, in particular those highlighted by the European Medicines Agency as particular eye disorders arising from unapproved IVT use of bevacizumab. Complications and side effects of treatment were typically infrequent or absent, and the majority of studies either made statements to this effect or reported zero cases of specific events.

No studies of the impact of bevacizumab on HRQoL were identified, and none of the studies eligible for the reviews of clinical effects and adverse effects reported HRQoL.

4.3 CONSIDERATIONS FOR IMPROVING THE FUTURE EVIDENCE BASE

- Current reporting within studies is variable and undermines confidence in the evidence presented.

- There were no data from controlled clinical trials or comparative studies on the effect of bevacizumab in patients with macular oedema secondary to RVO; the evidence came from non-randomised studies, largely from what appear to be before-and-after studies and case series.

- Poor reporting, ambiguities in the methodology and the composite nature of some studies obscure the true nature of the included studies and impede synthesis in review.

- Studies labelled by authors as case series, which feature near the bottom of the hierarchy of evidence, typically lacked the informality associated with this design and appeared protocol driven. These studies may therefore be of better quality than expected and warrant more attention.

- More controlled studies are required with more transparent reporting of methods.

- The wide variation and inconsistencies in reporting of the included studies, in particular the baseline characteristics of the participants, make it difficult to compare studies, draw valid conclusions and assess the generalisability of the results. Guidance for more consistent reporting of non-randomised studies, such as that provided by CONSORT (The CONSORT Statement. Accessed online via http://www.consort-statement.org December 2010) and The EQUATOR Network (Accessed online via http://www.equator-network.org December 2010) should be utilised.

- There is a need for more comprehensive, objective assessments of those events identified as adverse reactions in product information supplied by official agencies, in addition to underlying physiological parameters that can have a negative impact. More prominent surveillance and more formal reporting of adverse events could

alleviate concerns that particular adverse effects occurring within a study may go unnoticed.

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APPENDIX A

Included Studies

Included Studies Bibliography

1. Costa RA, Jorge R, Calucci D, Melo LA, Jr., Cardillo JA, Scott IU. Intravitreal bevacizumab (avastin) for central and hemicentral retinal vein occlusions: IBeVO study. Retina 2007;27(2):141-9.

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APPENDIX B

Excluded Studies

Excluded Studies Bibliography

Reference	Reason for exclusion
Abegg M, Tappeiner C, Wolf-Schnurrbusch U, Barthelmes D, Wolf S, Fleischhauer J. Treatment of branch retinal vein occlusion induced macular edema with bevacizumab. BMC Ophthalmology 2008;8:18.	Retrospective
Ach T, Hoeh AE, Schaal KB, Scheuerle AF, Dithmar S. Predictive factors for changes in macular edema in intravitreal bevacizumab therapy of retinal vein occlusion. Graefes Archive for Clinical & Experimental Ophthalmology 2010;248(2):155-9.	Retrospective
Ahmadi AA, Chuo JY, Banashkevich A, Ma PE, Maberley DAL. The effects of intravitreal bevacizumab on patients with macular edema secondary to branch retinal vein occlusion. Canadian Journal of Ophthalmology 2009;44(2):154-9.	Retrospective
Astam N, Batioglu F, Ozmert E. Short-term efficacy of intravitreal bevacizumab for the treatment of macular edema due to diabetic retinopathy and retinal vein occlusion. International Ophthalmology 2009;29(5):343-8.	Retrospective
Bakri SJ, Risco M, Edwards AO, Pulido JS. Bilateral simultaneous intravitreal injections in the office setting. American Journal of Ophthalmology 2009;148(1):66-9.e1.	Retrospective
Barone A, Russo V, Prascina F, Delle Noci N. Short-Term Safety and Efficacy of Intravitreal Bevacizumab for Pseudophakic Cystoid Macular Edema. Retina-the Journal of Retinal and Vitreous Diseases 2009;29(1):33-7.	Patients with RVO excluded from study. Retrospective.
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Byeon SH, Kwon YA, Oh H-S, Kim M, Kwon OW. Short-term results of intravitreal bevacizumab for macular edema with retinal vein obstruction and diabetic macular edema. Journal of Ocular Pharmacology & Therapeutics 2007;23(4):387-94.	Retrospective
Cheng KC, Wu WC, Chen KJ. Intravitreal triamcinolone acetonide vs bevacizumab for treatment of macular oedema secondary to branch retinal vein occlusion. Eye 2009;23(11):2023-33.	Retrospective
Chung EJ, Hong YT, Lee SC, Kwon OW, Koh HJ. Prognostic factors for visual outcome after intravitreal bevacizumab for macular edema due to branch retinal vein occlusion. Graefes Archive for Clinical & Experimental Ophthalmology 2008;246(9):1241-7.	Retrospective
Ehrlich R, Ciulla TA, Moss AM, Harris A. Combined treatment of intravitreal bevacizumab and intravitreal triamcinolone in patients with retinal vein occlusion: 6 months of follow-up. Graefes Archive for Clinical and Experimental Ophthalmology 2010;248(3):375-80.	Retrospective
Ferrara DC, Koizumi H, Spaide RF. Early bevacizumab treatment of central retinal vein occlusion. American Journal of Ophthalmology 2007;144(6):864-71.	Retrospective
Fish GE. Intravitreous bevacizumab in the treatment of macular edema from branch retinal vein occlusion and hemisphere retinal vein occlusion (an AOS thesis). Transactions of the American Ophthalmological Society 2008;106:276-300.	Retrospective
Fong KCS, Barry C, McAllister IL. Intravitreal bevacizumab (Avastin) as a treatment of the neovascular complications of laser-induced chorioretinal anastomosis for nonischaemic central retinal vein occlusion. Clinical and Experimental Ophthalmology 2009;37(5):485-9.	Case reports. Not specifically macular edema caused by RVO.
Forte R, Cennamo G, Vecchio EC, Tenore R, Aufiero B, de Crecchio G. Bevacizumab in macular edema. Functional and Anatomic	Results presented for patients with macular edema from different

Changes in a Prospective Case Series. Retina-the Journal of Retinal and Vitreous Diseases 2009;29(7):941-8.	aetiologies; results for patients with macular edema from RVO not reported separately.
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Kim JY, Park SP. Comparison between intravitreal bevacizumab and triamcinolone for macular edema secondary to branch retinal vein occlusion. Korean Journal of Ophthalmology 2009;23(4):259-65.	Retrospective
Krohne TU, Eter N, Holz FG, Meyer CH. Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans. American Journal of Ophthalmology 2008;146(4):508-12.	No relevant outcomes.
Matsumoto Y, Freund KB, Peiretti E, Cooney MJ, Ferrara DCAC, Yannuzzi LA. Rebound macular edema following bevacizumab (Avastin) therapy for retinal venous occlusive disease. Retina 2007;27(4):426-31.	Retrospective. Case reports.
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Rabena MD, Pieramici DJ, Castellarin AA, Nasir MaA, Avery RL. Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to branch retinal vein occlusion. Retina 2007;27(4):419-25.	Retrospective
Sakamoto A, Tsujikawa A, Ota M, Yamaike N, Kotera Y, Miyamoto K, et al. Evaluation of potential visual acuity in eyes with macular oedema secondary to retinal vein occlusion. Clinical & Experimental Ophthalmology 2009;37(2):208-16.	Study design (case series) not eligible for review of clinical effects; doesn't report adverse effects.
Shetty R, Pai SA, Vincent A, Shetty N, Narayana KM, Sinha B, et al. Electrophysiological and structural assessment of the central retina following intravitreal injection of bevacizumab for treatment of macular edema. Documenta Ophthalmologica 2008;116(2):129-35.	Mixed study sample; results not presented separately for those with macular edema from RVO.
Stahl A, Struebin I, Hansen LL, Agostini HT, Feltgen N. Bevacizumab in central retinal vein occlusion: a retrospective analysis after 2 years of treatment. European Journal of Ophthalmology 2010;20(1):180-5.	Retrospective
Tao Y, Hou J, Jiang YR, Li XX, Jonas JB. Intravitreal bevacizumab vs triamcinolone acetonide for macular oedema due to central retinal vein occlusion. Eye 2010;24(5):810-5.	Retrospective
Wong LJ, Desai RU, Jain A, Feliciano D, Moshfeghi DM, Sanislo SR, et al. Surveillance for potential adverse events associated with the use of intravitreal bevacizumab for retinal and choroidal vascular disease. Retina 2008;28(8):1151-8.	Retrospective
Wu L, Arevalo JF, Berrocal MH, Maia M, Roca JA, Morales-Canton V, et al. 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 2009;29(10):1396-403.	Retrospective
Wu L, Arevalo JF, Roca JA, Maia M, Berrocal MH, Rodriguez FJ, et al. Comparison of two doses of intravitreal bevacizumab (Avastin) for treatment of macular edema secondary to branch retinal vein occlusion: results from the Pan-American Collaborative Retina Study Group at 6 months of follow-up. Retina 2008;28(2):212-9.	Retrospective
Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, Arevalo JF, Berrocal MH, Farah ME, et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Archive for Clinical & Experimental Ophthalmology 2008;246(1):81-7.	Retrospective. Mixed study sample; unclear whether patients with RVO had macular edema. Results not reported separately for patients with RVO.
Wu WC, Cheng KC, Wu HJ. Intravitreal triamcinolone acetonide vs bevacizumab for treatment of macular oedema due to central retinal vein occlusion. Eye 2009;23(12):2215-22.	Retrospective
Yamaike N, Tsujikawa A, Sakamoto A, Ota M, Kotera Y, Miyamoto K, et al. Retinal sensitivity after intravitreal injection of bevacizumab for the treatment of macular edema secondary to retinal vein occlusion. Retina 2009;29(6):757-67.	Study design (case series) not eligible for review of clinical effects; doesn't report adverse effects.
Jonas JB, Libondi T, Schlichtenbrede F, Schmidbauer M. Intravitreal triamcinolone after intravitreal bevacizumab for retinal vein occlusions. Acta Ophthalmologica 2010;88(2):e24-e5.	Not relevant intervention (appears to be IVT triamcinolone given to non-responders to bevacizumab).
Russo V, Barone A, Conte E, Prascina F, Stella A, Noci ND. Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion. Retina 2009;29(4):511-5.	Randomised controlled study.

APPENDIX C

Study Specific Details Extracted from Included Studies

Extracted data describing the characteristics of the study and study population

Topic	Data extracted
Bibliographic details	Study ID (EndNote number) Study acronym First author Citation Year of publication Type of publication Country (of first author)
Study characteristics	Source of funding Study aims/objectives Study design (as described by authors) Length of study/follow-up Inclusion criteria Exclusion criteria Eligible outcomes for review Recruitment setting Recruitment procedure Total number of participants Total number of eyes Intervention Comparator(s) Intervention group: number of participants/eyes Control group: number of participants/eyes Withdrawals/exclusions/losses to follow-up Analysis: number of participants/eyes Statistical analysis Comments
Participant characteristics	Intervention group: mean age/age range Comparator group: mean age/age range Number (%) male/female Type of RVO Mean duration of RVO Degree of ischemia Severity/type of macular edema Glaucoma Other ocular disease Hypertension Lipid profile Diabetes mellitus Other risk factors or diseases Prior treatment Concomitant treatment Retreatment Additional information Comments
Quality assessment	Checklist for case series (6 questions) Study limitations (as acknowledged by authors)
Summary	Authors' conclusions

APPENDIX D

Objectives and Conclusions

Objectives and conclusions of the included studies

Author Year Country	Objectives	Authors' conclusions
Costa 2007 Brazil	To evaluate the safety, visual acuity changes, and morphologic effects associated with intravitreal bevacizumab injections for the management of macular edema due to ischemic central or hemicentral retinal vein occlusion.	Intravitreal bevacizumab injections of 2.0 mg at 12-week intervals were well tolerated and were associated with short-term best-corrected visual acuity stabilization or improvement and favourable macular changes in all patients with ischemic retinal vein occlusion and associated macular edema.
EUDRACT (Funk 2009; Kriechbaum 2009; Kriechbaum 2008; Prager 2009) Austria	To evaluate the efficacy and safety of intravitreal bevacizumab (Avastin) in eyes with macular edema secondary to central or branch retinal vein occlusion. To evaluate the association between functional and anatomic retinal changes during vascular endothelial growth factor therapy with bevacizumab (Avastin) in patients with cystoid macular edema secondary to retinal vein occlusion using microperimetry and spectral domain optical coherence tomography.	Intravitreal therapy using bevacizumab appears to be a safe and effective treatment in patients with macular edema secondary to retinal vein occlusion. However, the main limitations of this treatment modality are its short-term effectiveness and high recurrence rate. Vascular endothelial growth factor (VEGF) levels were significantly elevated in patients with central retinal vein occlusion compared with control subjects. Intravitreal injections of bevacizumab resulted in a substantial decrease of VEGF under physiologic levels and remained low under the loading dose of three consecutive monthly retreatments. Macular edema was related to VEGF levels in the aqueous humor. Central retinal morphology, especially central retinal thickness and central subfield thickness measured by conventional and SD-optical coherence tomography, and retinal function improved significantly during treatment of retinal vein occlusion with a flexible dosing regimen of intravitreal bevacizumab. Functional (central visual acuity and visual field) and morphologic parameters (retinal thickness) were significantly related. These associations highlight the value of optical coherence tomography imaging for assessing this disease entity. The double dose of the anti-vascular endothelial-growth factor agent was effective in eyes that did not fully respond to the preceding treatment with 1.25 mg. In eyes that responded to a lower dose treatment, but were switched to the higher dose after 6

Author Year Country	Objectives	Authors' conclusions
		months in accordance with the study protocol, the induced effect seemed more prolonged.
Gutierrez 2008 Spain	To evaluate efficacy and safety of intravitreal injections of bevacizumab in the treatment of macular edema secondary to retinal vein occlusion.	The authors did not draw any specific conclusions. They stated that their study demonstrates the early and clinically relevant benefits of bevacizumab injection for macular edema due to retinal vein occlusion: intravitreal injections of bevacizumab led both to a significant reduction of foveal thickness and an improvement of visual acuity. A beneficial effect was observed as early as the first week and over a 6-month follow-up period. The promising results indicate that further studies of intravitreal bevacizumab injection for the management of ischemic or non-ischemic retinal vein occlusion are justified.
Hoeh 2009 Germany	To evaluate the long-term outcome (6 months to 2 years) of an optical coherence tomography-guided reinjection scheme for bevacizumab treatment of macular edema due to retinal vein occlusion.	Patients with retinal vein occlusion benefit from treatment with bevacizumab. Favourable long-term results without necessity of further injections were achieved in 33% and 15% of central retinal vein occlusion and branch retinal vein occlusion patients respectively. The remaining patients needed repeated injections to treat macular edema recurrences. However, one third of the central retinal vein occlusion/branch retinal vein occlusion patients did not improve in visual acuity and further injections might be discontinued in these patients. In branch retinal vein occlusion and central retinal vein occlusion, treatment leads to a highly significant reduction of central retinal thickness and improvement of visual acuity.
Hung 2010 Taiwan	To evaluate the efficacy and safety of intravitreal bevacizumab (Avastin) injection in patients with macular edema secondary to retinal vein occlusive diseases.	The observed anatomic and visual acuity improvements after intravitreal bevacizumab injection demonstrate that bevacizumab is a useful adjunctive treatment for macular edema secondary to retinal vein occlusion without safety concerns in a short term. However, repeated injections are needed to maintain visual improvement. Long-term study is warranted to assess the long-term efficacy and safety and to determine the optimal dosing regimen.
Jaissle 2009 Germany	To investigate the long-term effectiveness of intravitreal bevacizumab treatment in eyes with perfused macular edema due to branch	Repetitive intravitreal bevacizumab injections result in a significant long-term improvement of visual acuity and central retinal thickness. The number

Author Year Country	Objectives	Authors' conclusions
	retinal vein occlusion.	of re-injections necessary to maintain this effect declined over time. However, the treatment seems to be only slightly better than grid laser photocoagulation.
Kondo 2009 Japan	To evaluate the 12-month follow-up results of intravitreal bevacizumab therapy for macular edema secondary to branch retinal vein occlusion and to identify the pretreatment factors that were associated with an improvement of the final visual outcome.	Intravitreal bevacizumab therapy can be a long-term effective treatment for macular edema secondary to branch retinal vein occlusion.
Kreutzer 2008 Germany	To evaluate the effect of intravitreal bevacizumab (Avastin) injections on visual acuity and foveal retinal thickness in patients with macular edema secondary to branch retinal vein occlusion.	Intravitreal injection of 1.25 mg bevacizumab appears to be an effective treatment option for eyes with branch retinal vein occlusion.
Moschos 2008 Greece	To evaluate by multifocal electroretinography and optical coherence tomography the effectiveness of intravitreal use of bevacizumab (Avastin) in the treatment of macular edema due to central retinal vein occlusion.	The intravitreal use of bevacizumab may provide anatomical and functional amelioration of the macula in patients with macular edema due to central retinal vein occlusion. However, further study is needed in order to assess the treatment's long-term efficacy.
Pai 2007 India	To investigate clinical, anatomic, and electrophysiologic response after single intravitreal injection of bevacizumab for macular edema attributable to retinal vein occlusion.	Intravitreal injection of bevacizumab appears to result in significant short-term improvement of visual acuity and macular edema secondary to vein occlusion. The present report confirms the previous studies. No ocular toxicity or adverse effects were observed. However, prospective, randomized, controlled long-term studies are required with an adequate number of patients.
Park 2009 South Korea	To investigate sequential changes of aqueous vascular endothelial growth factor and pigment epithelium-derived factor in macular edema secondary to branch retinal vein occlusion following intravitreal injection of bevacizumab.	Results indicate that aqueous vascular endothelial-growth factor (VEGF) levels are associated with persistent macular edema secondary to ischemic branch retinal vein occlusion following intravitreal injection of bevacizumab. High aqueous level of VEGF may be a poor prognostic factor after intravitreal bevacizumab. Persistent VEGF secretion overwhelming injected doses of bevacizumab may be involved in the pathogenesis of persistent macular edema associated with ischemic branch retinal vein occlusion after intravitreal bevacizumab.
Pournaras 2008 Switzerland	To assess the safety and efficacy of treatment of macular edema secondary to central retinal vein occlusion with intravitreal bevacizumab.	Treatment of macular edema secondary to central retinal vein occlusion with intravitreal bevacizumab injection of 1.25 mg was well tolerated and associated with marked macular thickness reduction and best-corrected

Author Year Country	Objectives	Authors' conclusions
		visual acuity improvement in all patients. A trend towards reduction of foveal thickness and improvement of visual acuity was observed in both acute and chronic central retinal vein occlusion.
Priglinger 2007 Germany	To evaluate the effect of intravitreal bevacizumab (Avastin) injections on visual acuity and foveal retinal thickness in patients with central retinal vein occlusion.	Intravitreal injection of bevacizumab appears to be a new treatment option for patients with macular edema secondary to central retinal vein occlusion.
Rensch (BRVO) 2009 Germany	To evaluate the effect of early intravitreal bevacizumab application in patients with macular edema due to non-ischemic branch retinal vein occlusion.	The present study suggests that an early intravitreal application of bevacizumab in patients with a non-ischemic branch retinal vein occlusion could lead to a significant increase in visual acuity and, correspondingly, to a decrease in macular edema.
Rensch (CRVO) 2009 Germany	To evaluate the effect of early intravitreal bevacizumab injections for the treatment of macular edema caused by non-ischemic central retinal vein occlusion.	Intravitreal bevacizumab injections given shortly after onset of non-ischemic central retinal vein occlusion may result in a significant increase in vision and a corresponding decrease in macular edema.
Sivkova 2010 Bulgaria	To evaluate the efficacy of intravitreal bevacizumab injection in reduction of the central macular edema in patients with diabetic retinopathy and branch or central retinal vein occlusion.	Bevacizumab seems to stimulate the reduction of the central macular edema in patients with diabetic retinopathy and retinal vascular occlusive disorders within the first 8 to 12 weeks. These results are encouraging and merit further long-term investigation in larger scale studies.
Stahl 2007 Germany	To evaluate the response to bevacizumab treatment in a prospective case series of retinal vein occlusion patients.	Bevacizumab injection is able to improve central macular edema and visual acuity in retinal vein occlusion patients within the first 3 to 9 weeks. We did not observe any short-term adverse effects during our study. As the decrease in visual acuity was anticipated by an increase in central retinal thickness, regular optical coherence tomography examinations between week 3 and 6 may be helpful for judging the appropriate timing for re-injection in order to maintain patients within the initially reached range of visual acuity until a new balance between inflow and outflow in the retinal circulation is reached.
Yamashiro 2010 Japan	To report 14 consecutive cases of endophthalmitis after intravitreal injection of bevacizumab (Avastin) obtained from a single batch.	Intravitreal injection of bevacizumab can cause sterile endophthalmitis. Most inflammation occurred within a few days after the intravitreal injection of the bevacizumab, but treatment with antibiotics, steroids, and/or vitrectomy was effective, and the prognosis was good in most cases.