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The safety of intravitreal bevacizumab monotherapy in adult ophthalmic conditions: systematic review

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ABSTRACT

Objectives: To assess the safety of intravitreal bevacizumab (IVB) as a monotherapy and to evaluate the relationship between quality of treatment and adverse events.

Data sources: Cochrane Library, Ovid MEDLINE, MEDLINE in-process, Ovid EMBASE and Toxicology Literature Online (TOXLINE) from January 2009 to May 2012. Studies included in an earlier systematic review were also assessed for inclusion.

Study eligibility criteria, participants and interventions: Randomised controlled trials (RCTs), controlled trials or observational studies including ≥10 participants reporting adverse events data following IVB monotherapy as a primary treatment in patients (aged 18 years or more) with any eye condition were included.

Study appraisal and synthesis methods: Study selection was undertaken independently by a minimum of two reviewers using pre-defined criteria. Data abstraction and quality assessment were performed by one reviewer, and then checked by a second reviewer. Study quality was assessed for only RCTs in accordance to the Cochrane Risk of Bias Tool. Additional items relating to safety data were also assessed. Results were tabulated or meta-analysed as appropriate.

Results: 22 RCTs and 67 observational studies were included. Only two RCTs reported valid safety data. Rates of serious adverse events following treatment were low. There was insufficient data to explore the relationship between the incidence of adverse events and quality of IVB injection.

Limitations: A majority of relevant existing studies were characterised by small sample sizes, unclear diagnostic criteria and reporting of safety outcomes.

Conclusions and implications of key findings: Available evidence demonstrates low rates of serious local and systemic adverse events following treatment. However, the role of IVB quality in the incidence of adverse events remains unclear. Robust evidence is needed to examine the relationship between the incidence of adverse events and variables such as injection techniques, pre-existing risk factors (eg, immunosuppression, cross-contamination) and quality of IVB treatment.

Strengths and limitations of this study

- Eighty-nine studies of bevacizumab monotherapy in patients with diverse ophthalmic conditions were included.
- A majority of relevant existing studies were characterised by small sample sizes, unclear diagnostic criteria and reporting of safety outcomes.
- The relationship between the incidence of adverse events and variables such as injection techniques, pre-existing risk factors (eg, immunosuppression, cross-contamination) and quality of bevacizumab could not be explored due to limited data.

INTRODUCTION

Age-related macular degeneration (AMD) and diabetic retinopathy (DR) have been identified as two of the three most common causes of age-specific visual impairment in England and Wales.[1] More recently, effective treatment options have included anti-vascular endothelial growth factors (anti-VEGFs), which have been shown to both delay deterioration in vision as well as improve vision.[2] Ranibizumab (Lucentis, Novartis) is licensed for the treatment of wet AMD and diabetic macular oedema (DMO) and costs £742.17 per injection (0.23 mL vial). Pegaptanib (Macugen; Pfizer) for treatment of AMD is available at a price of £514 per injection (300 µg vial). However, bevacizumab, which cost £242.66 for 4 mL/100 mg vial, is used as an unlicensed intervention in ophthalmic conditions. Although many doses for intravitreal administration can be produced from a single bevacizumab vial and therefore can be supplied for a much lower cost, the actual cost of dispensing smaller doses is uncertain. However, annual cost savings have been estimated if bevacizumab is used as standard treatment instead of ranibizumab in patients with AMD.[3]

Bevacizumab remains an unlicensed ophthalmic treatment for a number of reasons. There is an on-going debate with regard to intravitreal bevacizumab (IVB) use and its quality in clinical practice. One major concern relates to the risks associated with the reformulating the drug for intravitreal injections as well as possible adverse events (AEs) associated with systemically administered anti-VEGFs. Bevacizumab is reformulated for intravitreal use to deliver a smaller volume. However, the resulting reformulated product is considered by the Medicines and Healthcare products Regulatory Agency, a UK regulatory body for medicines and medical devices, as an unlicensed product. Another concern has centred predominantly on the possible risk of serious AEs such as endophthalmitis. To date, IVB safety evidence have been inconclusive.[4 5] The aim of this review was to assess the safety, in terms of rates of specific serious AEs, of IVB monotherapy in ophthalmic conditions.

METHODS

We updated an existing systematic review on AEs of intravitreal anti-VEGF reported by van der Reis *et al*,[5] which searched reports from 1948 to 2009. We adapted the search strategy by including specific AE terms and omitting selected terms because the previous search strategy:

- included fewer AE terms
- used broad terms such as 'cause' and 'response' and
- applied specific study design filters, for example, in vitro studies.

Free text and subject headings or thesaurus terms relating to the intervention (eg, bevacizumab, avastin) were combined with AE floating subheadings or specific AE terms. We searched the Cochrane Library; Ovid MEDLINE; MEDLINE in-process; Ovid EMBASE; and Toxicology Literature Online (TOXLINE) from January 2009 to May 2012 because this review was part of a project commissioned by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit (DSU) between April to August 2012. We did not search clinical trial registers. No experimental and functional study design filter or language restrictions were used. Our MEDLINE search strategy presented as an on-line supplementary file 1 was translated across different databases. Reference lists of all relevant studies and systematic reviews were checked and a citation search of relevant articles was also undertaken.

Study selection

Study selection was undertaken independently by a minimum of two reviewers using pre-defined criteria. Any disagreements in the selection process were resolved by consensus or referral to a third reviewer. All published or unpublished randomised controlled trials (RCTs), controlled trials or observational studies including ≥10 participants reporting AE data following IVB monotherapy as a primary treatment in patients (aged 18 years or more) with any eye condition were included. Relevant comparators were limited to monotherapies for RCTs only. Articles were excluded if patients had received prior treatment or received IVB as an adjunctive treatment. Non-English reports, narrative reviews, editorials, letters or publications relating to preclinical and biological studies were also excluded.

Data extraction and quality assessment

Data extraction and quality assessment were performed independently by one reviewer. Disagreements were resolved by discussion with a second reviewer and if agreement could not be reached, a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study. Information abstracted included study characteristics, participant details (eg, number of patients, eye condition, mean age and baseline comparability), intervention and comparator details (eg, source, dose, injection quality and frequency of treatment) and outcomes. Outcomes of interest were limited to important and serious ocular and systemic AEs as listed below:

Systemic AEs

- Death
- Hospitalisation
- Non ocular haemorrhage (gastrointestinal, pulmonary, other non-ocular bleeds)
- Arterial thromboembolism
- Hypertension
- Myocardial infarction
- Cerebrovascular accident (stroke)
- Transient ischaemic attack

Ocular AEs

- Infectious endophthalmitis (infection of the eye)
- Retinal detachment
- Retinal (pigment epithelium) tear
- Anterior chamber reaction (including acute intraocular inflammation; uveitis; inflammation of the anterior chamber and hypopyon)
- Ocular haemorrhage
- Lens damage/injury (including cataract, clouding of the lens)
- Ocular hypertension (raised intraocular pressure >21 mm Hg)
- Visual loss

For RCTs, study quality was assessed in accordance to the Cochrane Risk of Bias Tool. Additionally, we assessed items relating to safety data for RCTs; these included follow-up period greater than 6 months, definition of AE and description of method of ascertaining AE. A formal quality assessment was not undertaken for observational studies. While checklists exist for evaluating the methodological quality of a range of non-randomised studies, there is no consensus on how to incorporate a single tool to appraise different study types in a review.[6] It was anticipated that a variety of non-randomised study designs would be identified, so criteria assessed were

limited to study design (eg, prospective or retrospective), length of follow-up and baseline comparability when appropriate.

Data analysis

A pooled analysis was undertaken using the Cochrane Review Manager software where appropriate. The relative risk was calculated for dichotomous outcomes using a fixed effects model (Mantel-Haenszel method). Otherwise, descriptive statistics were tabulated. Estimates of AE rates were calculated by dividing the number of events by the number of patients who received IVB (event rate per patient) or the number of eyes treated (event rate per treated eye).

RESULTS

A flow chart of the study selection is shown in figure 1. Eighty-nine full text articles were included (n=22 RCTs, n=67 non-randomised studies). Of these 20 studies, including 1 RCT, were identified from the previous review. A total of 293 full text articles were excluded. Reasons for exclusion were wrong population, intervention or study type (n=162), unsuitable publication type (reviews, commentaries or editorials; n=34) and absence of usable data (n=97). A full list of excluded studies with reasons for exclusion is available on request.

Identified studies

A total of 22 RCTs comparing IVB with a variety of interventions as well as an observational control group with safety data were included, as presented in table 1.[2 7–27] Study populations were patients with AMD (n=7 studies); DMO (n=8 studies); retinal vein occlusion (RVO) (n=4 studies) and other ophthalmic conditions (n=3). Assessment of study quality is presented as an on-line supplementary file 2. Study quality was considered to be moderate to low with only two RCTs[16 19] meeting the criteria for valid safety data.

Sixty-seven observational studies were included as summarised in table 2. Most studies included patients with a single condition with fewer studies including a population with multiple conditions. Study quality was, generally, difficult to assess due to the quality of reporting. Approximately 65% of studies (n=44/67) were retrospective in design with follow-up periods of more than 6 months reported in less than a third (n=18/67) of included studies. Baseline characteristics of participants were comparable in two non-randomised studies[28 29] and three case-control studies.[30–32]

Treatment schedule and source

Administration of 1.25 mg/0.05 mL was the most commonly reported dosage of IVB. Frequency of dosing and follow-up schedules varied across studies. Information relating to the source of IVB was reported in 35% (n=14/22) of RCTs but less than a fifth (19%; n=13/67) of observational studies.[28 42–44 47 48 59 62 66 68 74 81 91] IVB was mostly provided by a local dispensing service such as the hospital's pharmacy. There were limited data to assess quality of administered IVB.

Reporting of AEs

Ascertainment of AEs was presented more objectively in RCTs compared to observational studies. Non-RCT evidence was unclear because several studies reported absence of events as 'no serious complications'; or 'no ocular complications', or 'no adverse events were observed', thereby providing limited information on diagnostic techniques or criteria for reported AEs. Furthermore, for AEs such as visual loss, ocular haemorrhage, hypertension and hospitalisation, the relationship between the outcomes and treatment schedule or setting remained largely unclear.

AEs reported in RCTs

Pooled 1-year data[16 19] indicated that the risk of death (RR 1.38; 95% CI 0.71 to 2.68) or arteriothrombotic events (RR 0.81; 95% CI 0.42 to 1.59) were not significantly different between patients with AMD who received IVB or intravitreal ranibizumab (IVR). Furthermore, no significant difference in death between the IVB and IVR arms was observed when the CATT[16] (2 year data) and IVAN[19] (1 year preliminary data) clinical trials were pooled to provide long-term data analyses as shown in figure 2. Cardiac disorders, transient ischaemic attack and hospitalisation for angina were not significantly different between patients with AMD treated with IVB and IVR.[19] However, serious systemic AE rates remained significantly lower in the IVR group (n=1795, RR 1.27 CI 1.09 to 1.47).

Two smaller studies, Biswas *et al*[15] and Gharbiya *et al*,[18] with safety data for patients with AMD reported no significant AEs. No significant differences were found for death and myocardial infarction (MI) in studies that compared IVB to pegaptinib[26] or sham injection[7] (n=232 patients, RR 0.30; 95% CI 0.01 to 7.18).

Rates for endophthalmitis were not significantly different between IVB and IVR treatment groups for patients with AMD (1 RCT; RR 1.79; 95% CI 0.53 to 6.08).[16] There were no reports of endophthalmitis,[9 11] ocular hypertension,[9 11] retinal detachment[2 9] or vitreous haemorrhage[9 11] in treatment groups comparing IVB with laser therapy in patients with DMO (n=269). In patients with DMO,[21 22 25] ocular hypertension (IOP>21 mm Hg) was significantly higher in the IVT group (n=183; RR 0.13; CI 0.02 to 0.69) compared with the IVB group. A similar but non-significant trend was demonstrated in patients with RVO (n=32 patients; RR 0.08; CI 0.00 to 1.25).[17]

One short-term study at 3 months[20] showed that posterior vitreous detachment was significantly higher in the IVB group compared with laser therapy (n=110; RR 17.00; CI 1.01 to 287.50). However, the rates of uveitis, vitreous haemorrhage, pigment epithelial tears and cataract progression were low and indicated no significant

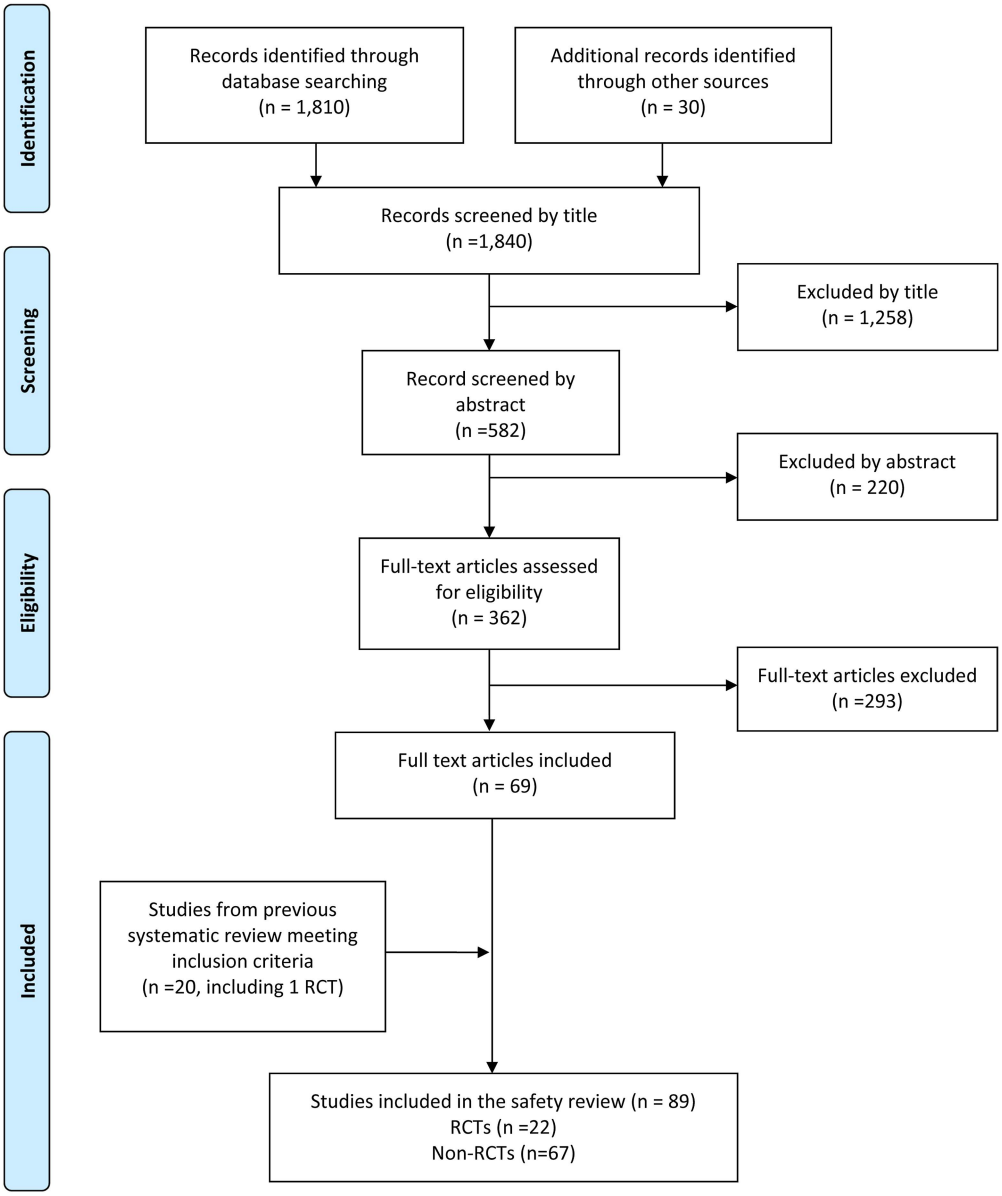

Figure 1 Summary of study selection. This flow chart outlines the process of study selection for the systemic review based on the recommendations of the PRISMA statement. RCT, randomised controlled trial.

differences between IVB and laser therapy. No significant differences in rates of foveal haemorrhage[13] (n=81; RR 0.62; 95% CI 0.28 to 1.35) or hyphema[27] (n=26; RR 7.8; 95% CI 0.46 to 131.62) were found in patients with RVO who had IVB or sham injection.

AEs reported in observational studies

Table 3, summarising safety data reported in observational studies, displays extensive variation in the detail of reporting of AEs with most studies not reporting or observing AEs of interest. While high event rates were reported for hospitalisation, hypertension, anterior chamber reaction and visual loss, these rates need to be interpreted with caution due to previously mentioned issues with reporting along with likely confounders.

Systemic AEs reported included death (0.4–3.8%),[40 48 54 94] arterial thromboembolism (0–1.4%),[81] hypertension (0–15.6%),[67 77 83 94] MI (0–8.2%),[28 45 81 94] cerebrovascular accident (0–8.7%)[39 45 54 83 94] and transient ischaemic attack (TIA) (0.4–1.0%).[40 81]

Visual loss was the most commonly reported ocular event,[28 32 35 50 53 56 69 89] the definition of visual loss was often unclear and occasionally associated with AEs such as anterior chamber inflammation, severe intraocular inflammation or retinal detachment. Consequently, it is uncertain whether visual loss occurred as an AE from treatment or progression of the patient's condition. Infectious endophthalmitis was reported in 10 studies (range 0–1.0%). Three of the 13 studies[28 42–44 47 48 59 62 66 68 74 81 91] in which patients received locally prepared IVB reported cases of infectious endophthalmitis. Reported rates were

Table 1 Summary of included randomised controlled studies

Study identifier, study location	Description of study population	Number of patients (eyes)	Interventions (treatment schedule and numbers treated)	Comparators (treatment schedule and numbers treated)	Reported safety outcomes	Information relating to preparation of intravitreal bevacizumab
Studies including patients with age-related macular degeneration (n=7 studies)						
Bashshur *et al*,[14] Lebanon	Neovascular age-related macular degeneration BCVA, 20/50 to 20/200 Submacular scarring or haemorrhage, sparing the fovea Mean age, 74.5 years	62 (NR)	IVB: 2.5 mg, mean 2.4 injections (n=32)	Laser therapy: mean 2.3 sessions (n=30)	Systemic adverse events Hypertension Outcomes at 6 months	IVB prepared in hospital pharmacy
Biswas *et al*,[15] India	Choroidal neovascularisation secondary to age-related macular degeneration BCVA, 35 to 70 ETDRS letter CMT, >250μm Mean age, not reported	60 (60)	IVB: 1.25 mg, 3 monthly injections, mean 4.3 (n=30)	IVR: 0.5 mg, 3 monthly injections, mean 5.6 (n=30)	Significant adverse events (unspecified) Outcome at 18 months	Methods of IVB preparation not reported
CATT 2012,[16] USA	Choroidal neovascularisation secondary to age-related macular degeneration BCVA, 20/25 to 20/320 Mean age, 79.5 years	1185 (1107)	IVB: 1.25 mg, monthly or as needed (n=586)	IVR: 0.5 mg, monthly or as needed (n=599)	Death Endophthalmitis Hypertension Adverse events associated with anti-VEGF treatment Arteriothrombotic adverse events Outcomes at 2 years	Re-packaging of commercially available bevacizumab into glass vials in an aseptic facility
IVAN 2012,[19] UK	Neovascular age-related macular degeneration; BCVA, ≥25 ETDRS letters Mean age, 77.0 years	610	IVB, 1.25 mg as continuous or as needed treatment at 3 separate visits (n=296)	IVR, 0.5 mg as continuous or as needed treatment at 3 separate visits (n=314 eyes)	Serious adverse events Death Arteriothrombotic events Transient ischaemic attack Hospitalised for angina Outcomes at 1 year	Commercially repackaged and prefilled syringes IVB
Lazic and Gabric,[20] Croatia	Minimally classic or occult choroidal neovascularisation secondary to age-related macular degeneration BCVA, ≥20/400 Mean age, 75.7 years	165 (165)	IVB, 1.25 mg (n=55)	1. Laser therapy: according to recommended standard procedures (n=55) 2. Combination treatment, that is, laser	Pigment epithelial tears Posterior vitreous detachment Thromboembolic events Cataract progression Outcomes at 3 months	Methods of IVB preparation not reported

Continued

Table 1 Continued

Study identifier, study location	Description of study population	Number of patients (eyes)	Interventions (treatment schedule and numbers treated)	Comparators (treatment schedule and numbers treated)	Reported safety outcomes	Information relating to preparation of intravitreal bevacizumab
				therapy followed by IVB, 1.25 mg within an hour (n=55)		
Schimid-Kubista *et al*,[24] Austria	Choroidal neovascularisation secondary to neovascular age-related macular degeneration BCVA, 5 to 40 ETDRS letters Mean age, 77.5 years	48 (48)	IVB, 1.0 mg every 6 weeks; total of 3 injections (n=13)	1. IVP, 0.3 mg every 6 weeks; total of 3 injections (n=18) 2. IVB, 1.0 mg then two injections of IVP 0.3 mg 6 weeks apart (n=17)	IOP Raised blood pressure Outcomes at 6 months	Methods of IVB preparation not reported
Tufail *et al*,[26] UK	Neovascular age-related macular degeneration; BCVA, 6/12 to 6/96 (Snellen equivalent) or 25 to 70 ETDRS letter scores Mean age, 81 years	131 (NR)	IVB, 1.25 mg, three loading injections at 6 week intervals followed by further treatment if required at 6 week intervals, mean injections 7.1 (n=65).	1. Laser therapy, (n=16) 2. IVP, 0.3 mg, (n=38) 3. Sham injection, (n=12)	Endophthalmitis Uveitis Retinal detachment Retinal tear Vitreous haemorrhage Lens damage Myocardial infarction Stroke Cerebral infarction Death Outcomes at 1 year	IVB injections were prepared as single use syringes with a shelf life of 6 weeks. Syringes were placed in sealed plastic pouches
Studies including patients with diabetic macular oedema (n=8 studies)						
Ahmadieh *et al*,[7] Iran	Diabetic macular oedema BCVA,≤20/40 Mean age, 59.7 years	101 (115)	IVB, 1.25 mg at baseline and weeks 6 and 12 (n=41 eyes)	1. IVB, 1.25 mg and IVT, 2 mg at baseline, then IVB, 1.25 mg at weeks 6 and 12 (n=37 eyes) 2. Sham injection (n=37 eyes)	Death Marked anterior chamber reaction Progression of fibrous proliferation Outcomes at 24 weeks	Methods of IVB preparation not reported
DRCRN 2007,[10] USA	Diabetic macular oedema (patients with type 1 and type 2 diabetes) BCVA, ETDRS VA letter score, 24 to78 (20/32 to 20/320) CMT ≥275 μm Median age, 65 years	109 (109)	1. IVB, 1.25 mg at baseline and week 6 (n=22 eyes) 2. IVB, 2.5 mg at baseline, week 6 (n=24 eyes)	1. Laser treatment at baseline (n=19 eyes) 2. IVB, 1.25 mg at baseline, laser treatment at week 3, then IVB, 1.25 mg at week 6 (n=22 eyes) 3. IVB, 1.25 mg at baseline, sham at week 6 (n=22 eyes)	Endophthalmitis, raised intraocular pressure, raised blood pressure, myocardial infarction, congestive heart failure Outcomes over a 70-week period	Methods of IVB preparation not reported

Continued

Table 1 Continued

Study identifier, study location	Description of study population	Number of patients (eyes)	Interventions (treatment schedule and numbers treated)	Comparators (treatment schedule and numbers treated)	Reported safety outcomes	Information relating to preparation of intravitreal bevacizumab
Faghihi *et al*,[11] Iran	Diabetic macular oedema (patients with type 2 diabetes) BCVA, ≤20/40 CMT, >250μm Mean age, 57.5 years	110 (130)	IVB, 1.25 mg, dosing schedule not reported (n = 42 eyes)	1. Laser (n = 47 eyes) 2. IVB (1.25 mg) + IVT (2 mg) (n=41 eyes)	Safety assessment Vitreous haemorrhage Ocular hypertension (≥23 mm Hg) Outcome 16 weeks	Methods of IVB preparation not reported
Lim *et al*,[21] Korea	Diabetic macular oedema BCVA, not reported CMT ≥300 μm Mean age, 60.0 years	111 (120)	IVB, 1.25 mg at baseline and at week 6 (n=36)	1. IVT, 2 mg (n=38) 2. IVB (1.25 mg)+IVT (2 mg) (n=37)	Hypertension Thromboembolic AE Serious ocular complications IOP Outcomes at 1 year	Methods of IVB preparation not reported
Marey and Ellakwa,[22] Egypt	Clinically significant diabetic macular oedema BCVA, not reported CMT at baseline, reported per study groups Mean age, 57.7 years	90 (90)	IVB, 1.25 mg (n=30)	1. IVT, 4 mg (n=30) 2. IVB (1.25 mg)+IVT (4 mg) (n=30)	IOP>22 mm Hg Cataracts Outcomes at 12 weeks	Methods of IVB preparation not reported
Michaelides *et al*,[9] UK	Clinically significant diabetic macular oedema (in patients with type 1 or type 2 diabetes) BCVA, 35 to 69 ETDRS letters CMT ≥279μm Mean age, 64.2 years	80 (80)	IVB, 1.25 mg at baseline, and then every 6 weeks as needed; number of injections ranged between 3 and 9 (n=42)	Laser therapy, every 4 months as needed; number of treatments, ranged between 1 and 4 (n=38)	Death IOP Loss of 30 ETDRS letters Vitreous haemorrhage Cerebrovascular accident Outcomes at 12 months	IVB prepared by Moorfields, London
Shahin *et al*,[25] Egypt	Diffuse diabetic macular oedema BCVA, not reported CMT ≥292μm Mean age, 52.7 years	32 (48)	IVB, 1.25 mg, single injection (n=24 eyes)	IVT, 4 mg, single injection (n=24 eyes)	IOP (≥23–43 mm Hg) Visually significant cataract Outcomes at 3 months	Methods of IVB preparation not reported
Soheilian *et al*,[2] Iran	Diabetic macular oedema BCVA, 20/40 to 20/300 CMT, not used as inclusion criterion Mean age, 60.5 years	129 (150)	IVB, 1.25 mg at baseline; treated repeated at 3 monthly interval on an as-needed basis (n=50 eyes)	1. IVB, 1.25 mg+IVT, 2 mg; treated repeated at 3 monthly interval on an as-needed basis (n=50 eyes)	Death Lens opacities IOP Vitreous haemorrhage High risk proliferative	Methods of IVB preparation not reported

Continued

Table 1 Continued

Study identifier, study location	Description of study population	Number of patients (eyes)	Interventions (treatment schedule and numbers treated)	Comparators (treatment schedule and numbers treated)	Reported safety outcomes	Information relating to preparation of intravitreal bevacizumab
				2. Laser therapy; treated repeated at 3 monthly interval on an as-needed basis (n=50 eyes)	diabetic retinopathy Outcomes at 2 years	
Studies including patients with retinal vein occlusion (n=4 studies)						
Cekic *et al*,[8] Turkey	Macular oedema due to branch retinal vein occlusion BCVA, ≤20/40 CMT, >250 μm Mean age, 63 years	21 (21)*	IVB: 1.25 mg, mean 1.6 injections (n=14)	IVT: 4 mg, mean 1.4 injections (n=17) IVT+IVB (n=21)	Endophthalmitis, uveitis, thromboembolic events Outcomes at 6 months	Methods of IVB preparation not reported
Ding *et al*,[17] China	Macular oedema secondary to retinal vein occlusion (unspecified) BCVA, ≤20/40 CMT, >250 μm Mean age, 54 years	31 (32)	IVB, 1.25 mg, repeat treatment given if condition persisted or recurred (n=16 eyes)	IVT, 4 mg, repeat treatment given if condition persisted or recurred (n=16 eyes)	IOP>21 mm Hg Outcomes at 9 months	Methods of IVB preparation not reported
Epstein *et al*,[12] Sweden	Macular oedema secondary to central retinal vein occlusion BCVA, 15 to 65 ETDRS letters (approx. 20/50 to 20/500) CMT ≥ 300μm	60 (60)	IVB, 1.25 mg at baseline and at weeks 6, 12 and 18 (n =30)	Sham injection: at baseline and at weeks 6, 12 and 18 (n=30)	Endophthalmitis Retinal tear Retinal detachment No serious non-ocular adverse events Outcomes at 6 months	IVB prepared in hospital pharmacy
Moradian *et al*,[13] Iran	Acute branch retinal vein occlusion BCVA, ≤20/50 Mean age, 57.6 years	81 (81)	IVB, 1.25 mg at baseline and 6 weeks (n=42)	Sham injection, at baseline and 6 weeks (n=39)	Foveal haemorrhage Foveal ischemia Outcomes at 12 weeks	Methods of IVB preparation not reported
Studies including patients with other ophthalmic conditions (n=3 studies)						
Gharbiya *et al*,[18] Italy	Pathologic myopia† BCVA, ≥26 ETDRS letters Mean age, 59.5 years	32 (32)	IVB, 1.25 mg at baseline, then given as needed (n=16 eyes)	IVR, 0.5 mg at baseline, then given as needed (n=16 eyes)	Systemic adverse events Endophthalmitis Retinal detachment Vitreous haemorrhage Hypertension IOP Outcomes at 6 months	Methods of IVB preparation not reported

Continued

Table 1 Continued

Study identifier, study location	Description of study population	Number of patients (eyes)	Interventions (treatment schedule and numbers treated)	Comparators (treatment schedule and numbers treated)	Reported safety outcomes	Information relating to preparation of intravitreal bevacizumab
Patwardhan *et al*,[23] India	Vitreous haemorrhage (grade 3 or 4), secondary to Earl's disease Mean age, 25.5 years	20 (20)	IVB, 1.25 mg every 4 weeks (n=10 eyes)	No active treatment (n=10 eyes)	Tractional retinal detachment Outcomes at 12 weeks	Methods of IVB preparation not reported
Yazdani *et al*,[27] Iran	Neovascular glaucoma BCVA ≥20/200 Mean age, 59.5 years	26 (26)	IVB, 2.5 mg; 3 injections given monthly (n=14 eyes)	Sham injection; 3 injections given monthly (n=12 eyes)	Hyphema Injection related adverse events Outcomes at 6 months	Methods of IVB preparation not reported

This table summarises the study characteristics of the 22 included randomised controlled studies. Data shown here include patient charateristics, interventions and outcomes reported in the included studies.
Calculation of mean age, when not specified, was based on the assumption that reported ages per treatment arms were normally distributed.
*The study population included 52 patients, of these 21 patients received a combination of intravitreal bevacizumab and intravitreal triamcinolone.
†This condition was defined as an axial length of at least 26.5 of subfoveal or juxtafoveal choroidal neovascularisation.
BCVA, best corrected visual acuity; CMT, central macular thickness; ETDRS, Early Treatment Diabetic Retinopathy Score; IOP, intraocular pressure; IVB, intravitreal bevacizumab; IVP, intravitreal pegaptinib; IVR, intravitreal ranibizumab.

0.02% (n=3/12 585 injections),[47] 0.2% (n=1/625)[62] and 0.8% (n=1/112).[42] A higher rate of 0.9% (n=1/109) was reported in a study with IVB supplied by a compounding pharmacy.[48] Positive cultures of microorganisms were reported in a study from Fong *et al*,[48] and another study from Wu *et al*.[94]

DISCUSSION

Eighty-nine studies were included in this systematic review of AEs, 22 of which were RCTs. Trials compared IVB with a number of different therapies and eye conditions, though most were in AMD, DMO and RVO. Most ocular and systemic safety measures had zero events in treatment groups or were not significantly different between groups. The quality of reporting of studies made it impossible to evaluate the impact of both known and unknown confounding factors (eg, the use of prophylactic antibiotic eye drops) on the incidence of AEs.

The most robust data for safety are from the CATT[16] and IVAN[19] trials which were large trials that reported longer term data. The results of these trials when meta-analysed revealed a statistically significantly higher rate of 1 or more serious systematic AE (RR 1.27; 95% CI 1.09 to 1.47) in the IVB group. In this analysis, the IVAN study[19] alone did not show a statistically significant difference while event rates were higher in the CATT. The recently published 2-year results of the IVAN study, which was not included in this review, has reported relatively worse safety outcomes for patients on discontinuous treatment compared to continuous treatment.[97] In addition, there were no observed differences in mortality, frequency of thrombotic events or hospitalisation due to cardiac failure between groups of patients treated with IVB or IVR. Reported pooled analysis of the 2 years results of the CATT and IVAN studies tends to demonstrate that IVB and IVR are comparable in terms of safety. It is also important to note that AEs were more common in those patients who received discontinuous rather than patients on continuous treatment, that is, those with lower exposure to the drug experienced higher AE rates. An explanation for this observation is the possible role of immunological processes in drug interactions.[97] It is also important to note that the CATT study demonstrated some imbalances at baseline between randomised patients which may need further exploration. More patients randomised to IVB had had a previous TIA compared to those in the IVR arms. Similarly, more IVB patients had a history of MI.[16] Despite these caveats, these trial designs offer the most robust assessment of AEs to date.

Overall, the evidence on IVB safety from observational studies was uncertain. This has previously been reported elsewhere.[4 5] Included studies were frequently associated with methodological weaknesses that limited the validity of the reported findings. The majority of studies were retrospective in design with small study samples or

Table 2 Summary of included observational studies

Author (year)	Study type	Condition (patients' mean age in years)	Number of patients (number of eyes)	Baseline comparability (yes/no/unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Abraham-Marin (2007)[33]	Case series, (prospective)	CNV due to AMD (76)	39 (39)	NA	2.5 mg	1	4 weeks	NR	NR	
Arevalo (2010)[34]	Case series, (retrospective)	CNV due to AMD	180 (207)	NA	1.25 mg (59.9%) 2.5 mg (40.1%) Frequency of dosing at discretion of treating physician	5.1 (per eye)	1, 3, 6, 12 and 24 months after the initial injection	NR	Arevalo-Coutinho Foundation for Research in Ophthalmology, Venezuela	
Artunay (2009)[35]	Case series, (retrospective)	Various* (NR)	NR (1822)	NA	1.25 mg once or repeated	NR	1–7 days, 4 weeks, 8 weeks	NR	NR	
Azad (2008)[36]	Non-randomised trial (prospective)	subfoveal CNV due to AMD (63)	40 (40)	NA	1.25 mg	2.4	6 months	NR	NR	
Baba (2010)[37]	Case series (retrospective)	Myopic CNV	40 (40)	Yes	1.25 mg	1.3 to 1.5	24 months	NR	NR	Treatment groups: PDT (n=16); PDT and IVB (n=12); IVB only (n=12)
Bakri (2009)[38]	Case series, (retrospective)	Various† (NR)	35 (70)	NA	1.25 mg	5.9	39 days	NR	The Research To Prevent Blindness, New York	
Bashshur (2009)[28]	Nonrandomised trial, open-label, prospective (extension study)	CNV due to AMD (72.2)	51 (51)	NA	2.5 mg	2.5 (3.4 during first 12 months, decreased to 1.5 during second year)	24 months	local dispensing service	American University of Beirut Medical Center	
Carneiro (2010)[39]	Cohort, (prospective)	Subfoveal or juxtafoveal CNV secondary to AMD (76.9)	(80)	NR	1.25 mg	4	6 months, 12 months	NR	Sociedade Portuguesa de Oftalmologia, Hospitalde Sao Joao,	
Carneiro (2011)[40]	Cohort (retrospective):IVB vs IVR	AMD (77.8)	97 (IVB group)	Yes (IVB:IVR)	1.25 mg;	7.8	2.3 years	NR	Sociedade Portuguesa de Oftalmologia, Hospitalde Sao Joao, Swiss National Foundation and Walter and Gertrud Sienenthaler Foundation	Increased rate of ATEs in IVB group compared to IVT (secondary analyses
Chen (2010)[41]	Non-randomised cohort (retrospective)	MO due to BRVO (60.7)	24 (25)	Yes (IVB:IVT:control; n=83)	2.5 mg single injection then as needed	NR	10 months (mean)	NR	NR	Patients received IOP-lowering treatment during follow-up period if IOP ≥21 mm Hg. Anterior paracentesis was performed before IVB to reduce ocular pressure.

Continued

Table 2 Continued

Author (year)	Study type	Condition (patients' mean age in years)	Number of patients (number of eyes)	Baseline comparability (yes/no/unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
										Author's conclusion: IVB better than IVT
Cleary (2008)[42]	Case series (retrospective)	Neovascular AMD (75)	111 (112)	NA	1.25 mg, once then as needed	NR	4.9 (range 1–12)	Local dispensing service	None	
Costa (2006)[43]	Non-randomised dose escalation study (prospective)	CNV caused by AMD (74.6)	45 (45)	Yes (1.0 mg:1.5 mg:2.0 mg)	1.0 mg, 1.5 mg and 2.0 mg	NR	3	Local dispensing service	Public funding (Foundation for Research Support of the State of São Paulo)	Reported as a dose escalation study but difficult to tell how many doses each participant was given and how far apart
Costagliola (2009)[44]	Case series (retrospective)	CNV (subfoveal) due to AMD (73.2)	68 (68)	NA	1.25; then monthly as per needed	3.87 (first 6 months); 1.09 (for remaining 6 months)	12	Local dispensing service	NR	Exclusion criteria included previous history of thromboembolic events; uncontrolled hypertension, BP >150/90 mm Hg. Topical antibiotics prescribed for 3 days, after injection
Curtis (2010)[45]	Cohort (retrospective)	AMD (median, 81.0)	27 962 (IVB only; n=146 942)	Yes (IVB:PDT: IVP: IVR)	NR	NR	12 months	NR	Research agreement between OSI Eyetech and Duke University	Patient data were censored when at the time when a treatment which was different from initially assigned intervention was received. Between July and December 2006, study population was limited to treatment-naïve patients who received bevacizumab or ranibizumab
Falkenstein (2007)[46]	Case series (prospective)	AMD (79.4)	70 (NR)	NA	1.25 mg assumed (0.05 mL)	1.74 (calculated from 122 injections for 70 patients)	3,10 and 15 minutes	NR	NR	

Continued

Table 2 Continued

Author (year)	Study type	Condition (patients' mean age in years)	Number of patients (number of eyes)	Baseline comparability (yes/no/unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Fintak (2008)[47]	cohort (retrospective)	Various (NR)	12 585 (IVB injections)	NR	1.25 mg	NR	5 days	Local dispensing service	NR	Number of injections not reported
Fong (2008)[48]	Case series (retrospective)	AMD (82)	109 (109)	NA	1.25 mg, three consecutive monthly injections then as needed	NR	9.4 months (range 6-12)	Compounding pharmacy	NR	
Frenkel 2010[49]	Cohort (retrospective)	AMD (80)	47‡	Unknown (IVB: ranibizumab: pegaptanib)	1.25 mg	1	20 minutes	NR	NR	First injection only selected for the study
Fukami (2011)[50] (abstract)	Case series (retrospective)	NR (NR)	12 (12)	NA	NR	NR	2 days	NR	NR	
Gamulescu (2010)[51]	Cohort (retrospective)§	AMD (77.5)	30 (NR)	NR	1.25 mg every 4 weeks 3 initial injections	NR	2-4 months after last injection	NR	NR	
Gomi (2008)[52]	Case series (Retrospective)	Polypoidal choroidal vasculopathy (65.4)	11 (11)	NA	1 mg¶ once or as needed	NR	9.4 months (±4.4)	NR	NR	
Good (2011)[31]	Cohort (retrospective)**	AMD (76.6)	NR (101)††	Yes	1.25 mg	7.0	86.6 days mean	NR	NR	
Goverdhan (2008)[53]	Case series (retrospective)	CNV due to AMD (79.5)	53 (53)	NA	1.25 mg Repeat injections offered if CNV persisted or fresh haemorrhage or subretinal fluid observed.	1.36	Day 1 and after 2 week visits then at 4-week intervals. Minimum 6 months (range 4 to 12 months)	NR	NR	
Gower (2011)[54] (abstract)	Cohort (retrospective)	Neovascular AMD (NR)	NR (NR)	NR (IVB:IVR)	NR	NR	NR	NR	NR	HRs adjusted for baseline comorbidities, demographics and socio-economic status
Hernandez-Rojas (2007)[55]	Case series (prospective)	CNV due to pathological myopia (53.9)	13 (13) (at follow-up—one patients lost to follow-up)	NA	2.5 mg/0.1 mL once or as needed	NR	3 months	NR	NR	
Higashide (2012)[56]	Case series (retrospective)	Neovascular glaucoma (63.5)	70 (84)	NA	1.25 mg	1.4	3 months	NR	NR	
Hollands (2007)[57]	Case series (prospective)	Neovascular AMD (84.6%); DMO (6.7%); Others—histoplasmosis (8.7%) (76)	104	NA	1.25 mg	NR	30 min	NR	NR	

Continued

Table 2 Continued

Author (year)	Study type	Condition (patients' mean age in years)	Number of patients (number of eyes)	Baseline comparability (yes/no/unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Ikuno (2009)[58]	Case series (retrospective)	CNV due to myopia (58.4)	63 (63)	NA	1 mg	2.4	12 months	NR	The Ministry of Education, Culture, Sports Science and Technology of Japan; Health and Labor Sciences Research of Japan	Re-injection considered after 2–3 months if fluorescein leakage in angiograam or subretinal fluid persisted
Inman (2011)[59]	Case series (retrospective)	NR	608 (sample included patients that received IVB, IVP and IVR)	NA	NR	Unclear (1841 injections of IVB, 428 IVP and 2421 IVR)	4.4 years	Local dispensing service	NR	This study reported incidence of infectious endophthalmitis associated with 2% topical lidocaine gel anaesthesia. No information on conditions being treated or patient demographics.
Jaissle (2009)[60]	Case series (prospective)	MO due to BRVO (median, 68)	23 (23)	NA	1.25 mg (re-injection considered if macular oedema persisted in foveal area and visual acuity 20/32 or worse)	NR	1 year. (examined every 6 weeks)	NR	German Opthalmological Society	During the 1-year follow-up, an average of 2.4 re-injections (range, 0–5) were administered, with a mean of 1.6 re-injections within the first 6 months (weeks 6–24) and a further 0.8 re-injections over the latter 6 months (weeks 30–48).
Johnson (2010)[61]	Case series (retrospective)	Various‡‡ (76.5)	173 (193)	NA	NR	3.98	Median follow-up; 40 days (range 19 to 170 days)	NR	Queen's University, Canada	
Jonas (2007)[62]	Case series (retrospective)	AMD	625 (684)	NA	1.5 mg	1.95	≥4 weeks	Local dispensing service	NR	534 re-injections
Jonas (2008)[63]	Case series (retrospective, consecutive)	Various	NR (3818 IVB injections)	NA	1.5 mg	NR	≥3 months	NR	None	
Julian (2011)[64]	Case series (retrospective)	CNV due to uveitis (median, 41.9)	15 (15)	NA	1.25 mg (re-treatment based on signs of active neovascularisation)	4.25	17.6 (median)	NR	NR	In all cases, optimum control of intraocular inflammation was achieved by the time IVB was initiated

Continued

Table 2 Continued

Author (year)	Study type	Condition (patients' mean age in years)	Number of patients (number of eyes)	Baseline comparability (yes/no/unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Kim (2009)[32]	Before–after study of IVB group and triamcinolone acetonide group (retrospective)	MO due to BRVO (56.9)	50 (50) (22 received IVB and 28 received triamcinolone acetonide)	NA	1.25 mg single dose	NR	24 weeks	NR	NR	NR
Kim (2011)[65]	Case series (retrospective)	DMO	48 (65)	Yes	1.25 mg	NR	≥12 months	NR	Grant from Kyung Hee University	
Kim (2011)[29]	Non-randomised controlled study (prospective, consecutive)	AMD, RVO, DMO (64.8)	60 (60)	Yes	1.25 mg	1	NR	NR	NR	
Kiss (2006)[66]	case-control (retrospective)§§	AMD (NR)	61	Yes	1 mg	1	7 days	Local dispensing service	NR	
Krebs (2009)[67]	Case series (prospective)	AMD (NR)	44 (44)	Unknown	1.25 mg 3 monthly injections based on OCT and FA findings	2.6	1 week, 1 month and 3 months	NR	L. Boltzmann Institute	
Kriechbaum (2008)[68]	Case series (prospective)	MO due to BRVO or CRVO (66)	28 (29)	Unknown	1 mg at 4-week intervals 3 intravitreal injections	5.3	1, 7 and 28 months	Local dispensing service	NR	
Krishnan (2009)[69]	Case control (retrospective) ¶¶	CNV due to AMD (80.5)	14	No	1.25 mg	NR	2 and 4 weeks	NR	NR	
Kumar (2012)[70]	Case series (retrospective)	Eales' disease (median, 33)	14 (14)	Unknown	1.25 mg	1	3 months	NR	NR	
Lazic (2007)[71]	Case series (prospective)	CNV secondary to AMD	102 (102)	NA	1.25 mg, once then as needed	NR	≥1.5 months	NR	None	Follow-up was 6-weekly and ongoing
Lima (2009)[72]	Retrospective cohort study	Various, mostly AMD	326 (IVB injections)	NR	NR	NR	NR	NR	Macula Foundation Inc.	Same-day bilateral injections
Lommatzsch (2009)[73]	Case series (retrospective)	AMD (77.7)	86	NR	1.25 mg at 6 week intervals	NR	42.4 weeks	NR	NR	
Lorenz (2010)[74]	Case series (retrospective)	Various***	144 (145)	Yes	1.25 mg	1.63	14	local dispensing service	None	
Mason (2008)[75]	Case series (retrospective)	Various†††	NR	NR	1.25 mg	NR	NR	NR	University research grant, New York.	
Manayath (2009)[76]	Case series (prospective)	CMO due to CRVO 15 (64)	15	No	1.25 mg	2.2	6-18 months	NR	NR	
Rasier (2009)[77]	Quasi-experimental ‡‡‡	AMD (67.2)	82	Unknown	1.25 mg	1	6 weeks	NR	NR	
Russo (2009)[78]	Non-randomised controlled trial	MO due to BRVO	15 (15)	Yes (IVB:LGP)	1.25 mg, once or repeated as necessary	NR	12 months	NR	NR	No. of eyes/patients refers to IVB group
Saeed (2011)[79]	Cohort (prospective)	Retinal vascular occlusions and other causes of CMO (68.6)	18	NA	1.25 mg	NR	NR	NR	NR	Authors reported that nti-VEGF related reflux was not associated with a sub-therapeutic effect

Continued

Table 2 Continued

Author (year)	Study type	Condition (patients' mean age in years)	Number of patients (number of eyes)	Baseline comparability (yes/no/unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Shah (2011)[80]	Cohort (retrospective)	Various	10 958 (IVB injections)	NR	NR	NR	6 days	NR	NR	
Sharma (2012)[81]	Cohort (retrospective)	AMD, DMO RVO (IVB group,76.9)	173 (693 IVB injections)	No difference in age and VA (IVB:IVR)	1 mg	unclear	NR	Local dispensing service	Part-funded by Novartis (and part-funded by Canadian Institutes for Health Research)	IVR patients were on average 1.8 years older than IVB patients (78.7 vs 76.9, p 0.01) and had slightly worse baseline vision (6/76 vs 6/64, p 0.013). 195 out of the 351 patients that received IVR, had been treated previously with IVB (mean, 4.3 injections per patient). Prior treatment in IVB group unclear
Shienbaum (2012)[82]	Case series (retrospective)	AMD	73 (74)	Yes (IVB:IVR)	NR (Monthly treatment until no intraretinal or subretinal fluid on optical coherence tomography. Treatment intervals determined by signs of exudation	NR	1.41 years	NR	None reported	
Shima (2008)[83]	Case series (retrospective)	Various§§§	707 (1300 injections)	NR	1 mg Once or repeated injections	NR	≥2 months	NR	Health Sciences Research Grant, Ministry of Health, Labour and Welfare, Japan	
Shimada (2011)[84]	Case series (retrospective)	Myopic CNV (58.4)	74 (74)	NA	1.25 mg At baseline, week 1, then monthly (unspecified length of time)	NR	12 months (SD-4.3)	NR	Grants 19390441 and 19659445 from the Japan Society for the Promotion of Science, Tokyo, Japan	
Sivkova (2010)[85]	case series (prospective)	CME due to DR, BRVO and CRVO (DR patients 59.7; RVO patients, 68)	96 (107)	Unclear (DR:RVO)	1.25 mg 3 consecutive injections at 1-monthly intervals	NR	4 months	NR	NR	No significant difference in adverse events between groups
Sohn (2011)[86]	Case control (prospective) ¶¶¶	DMO (54.5)	11	NA	1.25 mg	NR	1.3 months	NR	GachonUniveristy, Incheon Korea	

Continued

Table 2 Continued

Author (year)	Study type	Condition (patients' mean age in years)	Number of patients (number of eyes)	Baseline comparability (yes/no/unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Song (2011)[87]	Case control (retrospective)****	DMO (57.1)	35 (58)	Yes (IVB:IVT)	1.25 mg	NR	8 weeks	NR	Institute for Medicine research grant of Kosin University College of Medicine	
Sonmez (2011)[88]	Case series (prospective)	Subfoveal CMO due to AMD (69.4)	24 (24)	NA	1.25 mg weeks 0, 6 and 12, then every 12 weeks until week 48	5	NR	NR	NR	Of 27 patients, 3 were lost to follow-up/protocol violation)
Spandau (2006)[89]	Case series (retrospective, consecutive)	AMD	63	NA	1.5 mg	NR	≥2 months	NR	NR	
Torres-Soriano (2012)[90]	Case series (prospective)	CNV PDR, RVO (NR)	31	NA	2.5 mg, frequency not reported	1.3	1 month	NR	NR	
Valmaggia (2009)[91]	Case series (retrospective)	CNV due to AMD (75.5)	324	NA	1.25 mg; then every 6 weeks. Frequency not reported	3.3	NR	Local pharmacy	NR	
Weinberger (2007)[92]	Case series (retrospective)	PED in exudative AMD (76)	31 (31)	NA	1.25 mg once	NR	1–7 months	NR	Academic institution	
Wickremasinghe (2008)[93]	Case series (retrospective)	Neovascular AMD	1278 IVB injections	NA	1.25 mg	NR	1 week	NR	NR	
Wu (2008)[94]	interventional case series (prospective)	Various (including RVO, DMO)	1173 (1310)	NA	1.25 mg (16%), 2.5 mg (89%)	3.7 (3.3 per eye)	12–15 (13.6)	NR	No	
Yoon (2012)[95]	Case series (retrospective)	Myopic CNV (49)	26	NA	1.25 mg	2.2	12 months	NR	NR	Of the 40 patients included in the study, 14 received IVR
Zhang (2012)[96]	Non-randomised interventional case series (prospective)	Subfoveal idiopathic CNV (32)	40	NA	1.25 mg	2	12 months	NR	NR	

This table summarises the study characteristics of included observational studies.Data shown here include patient charateristics, interventions and outcomes reported in the included studies.
*Artunay 2009[35] studied patients with the following conditions: AMD, CNV due to myopic degeneration idiopathic and other secondary causes, cystoid or diffuse MO from CRVO, BRVO, diabetes, uveitis and retinitis pigmentosa proliferative retinopathies.
†Population included patients CNV due to AMD, DMO, DR, MO due to RVO or autoimmune retinopathy.
‡Forty-seven patients out of a study population of 71 received bevacizumab. A number of patients received all three anti-VEGF medications while others received just one treatment type. However, authors reported that only the first anti-VEGF injection was considered in the study.
§Gamulescu (2010)[51] included a control group that received ranibizumab.
¶Re-injection in five eyes, 1 or 2 months after first injection at physician discretion.
**Good *et al*[31] included a control group that received ranibizumab.
††101 eyes received bevacizumab only, 96 eyes received ranibizumab only and 18 eyes received bevacizumab and ranibizumab.
‡‡Population included patients AMD, diabetes, retinal vein occlusion and other eye conditions.
§§Kiss *et al*[66] included a control group that received triamcinolone acetonide.
¶¶Krishnan *et al*[69] included a control group that received ranibizumab.
***Population included patients with AMD, BRVO, CRVO and myopic choroidal neovascularisation.
†††Population included patients with neovascular AMD; BRVO, CRVO; cystoid macular oedema; proliferative DR and DMO.
‡‡‡Rasier *et al*[77] reported between-group comparison of hypertensive/non-hypertensive patients.
§§§Conditions included AMD, DR, CNV, BRVO, CRVO and other pathologies (unspecified).
¶¶¶Control group received triamcinolone acetonide.
****Control group received triamcinolone acetonide.
AMD, age-related macular degeneration; BP, blood pressure; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CMO, cystoid macular oedema; CNV, choroidal neovascularisation; DMO, diabetic macular oedema; DR, diabetic retinopathy; FA, fluorescein angiography; IVB, intravitreal bevacizumab; IVP, intravitreal pegaptinib; IVR, intravitreal ranibizumab; MO, macular oedema; NA, not applicable, NR, not reported; OCT, optical coherence tomography; PDT, photodynamic therapy; RVO, retinal vein occlusion; PED, pigment epithelium detachment.

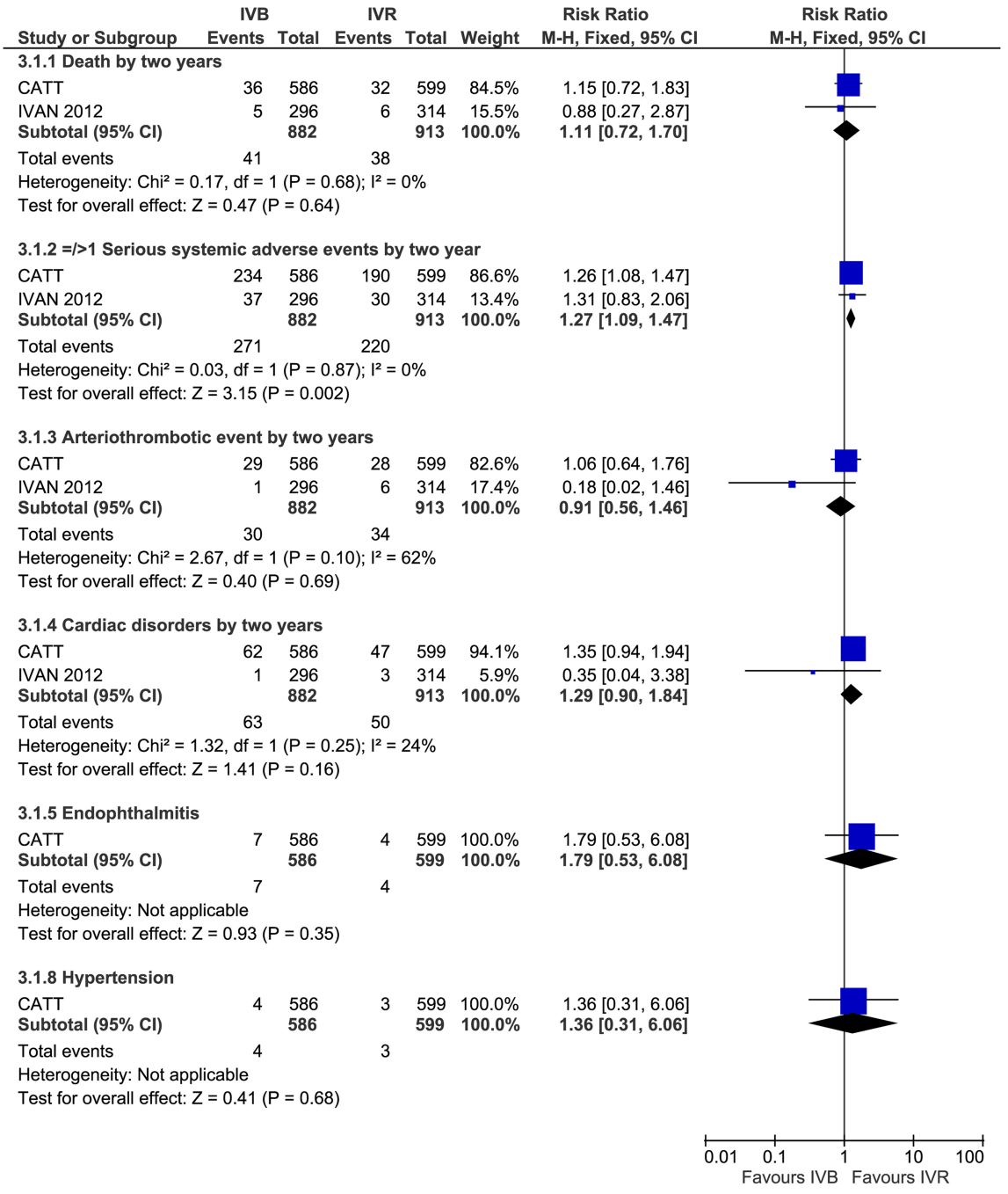

Figure 2 Pooled analysis of systemic adverse events comparing intravitreal bevacizumab with intravitreal ranibizumab in patients with age-related macular degeneration. This figure shows the pooled effect estimate for systemic adverse events comparing intravitreal bevacizumab with intravitreal ranibizumab in patients with age-related macular degeneration. IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab. This figure has been reproduced from the full report related to this project available at http://www.nicedsu.org.uk/Bevacizumab%20report%20%20NICE%20published%20version%2011.04.13.pdf.

inadequate follow-up periods (less than 6 months). With respect to larger studies, observational data from Curtis *et al*.[45] suggest no difference in the risk of AEs between IVB and IVR once socioeconomic confounders are accounted for. On the other hand, results of an unpublished study of Medicare patients funded by Genentech[54] found an increased risk of stroke and death in IVB patients. The available abstract, however, did not provide sufficient information to allow an in-depth analysis of the results of this study. A recently published population-based, nested case-control study reported by Campbell *et al*[98] (n=91 378) found no relationship between the risk of MI, venous thromboembolism, stroke or congestive heart failure and the administration of IVR or IVB. While the risk of systemic AEs was similar for both treatment groups, there was an increased risk of acute MI for a subgroup of patients with diabetes who received IVB.

Table 3 Serious systemic and ocular adverse events reported in included observational studies

Adverse event	Rates (%)	Number of eligible studies contributing data	Percentage of eligible studies reporting zero events
Systemic adverse events			
Death	0.4 to 3.8	6*	Not applicable
Hospitalisation	32†	1	Not applicable
Non-ocular haemorrhage	0.0	1	100%(n=1)[82]
Arterial thromboembolism	0.0 to 1.35‡	9	78% (n=7)[34 38 44 82 85 88 96]
Hypertension	0.0 to 15.6	9	44% (n=4)[42 43 82 96]
Myocardial infarction	0.0 to 8.2	10	50% (n=5)[34 38 56 67 82]
Cerebrovascular accident	0.0 to 8.7	11§	45% (n=5)[34 38 56 67 82]
Transient ischaemic attack	0.4 to 1.0	5[34]	60% (n=3)[34 67 82]
Ocular adverse events			
Infectious endophthalmitis	0.0 to 1.0	31¶	62% (n=19)[29 32 41 43 44 51 56 59 60 65 67 73 76 81 85 86 88 91 96]
Retinal detachment	0.0 to 29.0	20	75% (n=15)[29 32 35 56 65 67 68 76 79 81 85 86 91 95 96]
Retinal tear	0.0 to 15.0	14	42% (n=6)[29 44 52 60 65 85]
Anterior chamber reaction	0.0 to 50.0	21**	57% (n=12)[29 41 43 44 51 56 67 68 85 88 91 96]
Ocular haemorrhage	0.0 to 72.0	14	43% (n=6)[32 41 52 56 85 91]
Lens damage	0.0 to 0.5	9	67% (n=6)[41 56 65 67 85 91]
Ocular hypertension	0.0 to 20.0	16††	50% (n=8)[29 32 36 41 65 70 87 91]
Visual loss	0.0 to 50.0	9	11% (n=1)[85]

Estimates of adverse event incidence were calculated by dividing the number of reported events by the number of patients that received IVB (event rate per patient) or the number of eyes treated (event rate per treated eye).
*One study presented an HR of 1.11 (99% CI 1.01 to 1.23, IVB vs IVR).
†Incidence of systemic adverse events was reported based on number of injections and not patients, 32% (n=222/693 injections).
‡Event rate was presented for a sub-group to the study population living in a specified geographical area.
§ One study reported an HR of 1.57 (99% CI 1.04 to 2.37, IVB vs IVR).
¶Authors of one study stated that the rate of infectious endophthalmitis after an IVB injection of 1.5 mg may be approximately 1:1000.
**One study reported an HR of 1.8 (99% CI 1.2 to 2.8, IVB vs IVR).
††One study reported an HR of 0.81 (99% CI 0.71 to 0.93, IVB vs IVR).

This review highlighted the challenges of assessing the safety of IVB especially due to limited opportunities for in-depth detailed analyses of the relationship between IVB preparation and reported rates of infectious endophthalmitis. In the past, case reports have suggested contaminated batches of IVB as the primary source of infection; a published review of patient safety information held by the National Patient Safety Agency in England and Wales[99] reported an increased risk of serious AEs including endophthalmitis following IVB treatment. The authors acknowledged that identifying the source of infection (ie, contaminated injection procedure or infected anti-VEGF) could be complex. However, Jonas *et al*,[63] reporting on AE rates in a study population which included patients who had received IVB and IVT, suggested that event rates were statistically independent of drug injected (p=0.45), operating surgeon (p=0.18) and patient's age (p=0.87).

It is also important to highlight limitations of this review. By relying on the previous systematic review[5] as a source of evidence, it is possible that studies that were not identified in that review may have been missed in this review. Our searches were undertaken up to 2012. An updated electronic literature search was conducted up to 23 May 2014, retrieving a total of 1300 records. A preliminary shift of titles resulted in 333 potentially relevant abstracts for further detailed examination. We would prefer to have undertaken a full update. Unfortunately, this is not possible for us at present due to lack of the extensive time and resources required. Although comprehensive and up-to-date systematic reviews are desirable, a recent analysis of a sample of systematic reviews showed that the median duration of survival indicating a requirement for an update was 5.5 years (95% CI 4.36 to7.67) in systematic reviews of randomised trials of procedures or conventional drugs.[100] Furthermore, many RCTs randomised small numbers of participants and these may have been underpowered to detect differences in AEs.[4 97] Generalisability of findings may also be limited due to

differences between study participants and patients seen in routine practice. In addition, there were concerns relating to ascertainment of exposure particularly in observational studies.[98] The influence of excluding non-English publications in this review is unclear. Additionally, adopting a narrow focus in the definition of AEs implies that data on less serious or rare events were not presented.

CONCLUSIONS

Overall, rates of serious AEs following IVB were low when compared to other intravitreal treatments, sham injection and laser therapy with relatively higher rates being reported in head-to-head studies of IVB versus ranibizumab. Most outcomes were, however, not significantly different between treatment groups. Current evidence from observational data still remains limited due to relatively small sample sizes, unclear definition, evaluation and reporting of safety outcomes as well as adequate follow-up periods. However, an opportunity to explore the relationship between the incidence of AEs and other variables such as injection techniques, pre-existing risk factors (eg, immunosuppression, cross-contamination) and quality of IVB could offer cost-saving options in providing treatment for certain ophthalmic conditions.

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The safety of intravitreal bevacizumab monotherapy in adult ophthalmic conditions: systematic review

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