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Christine Schmucker, Yoon K. Loke, Christoph Ehlken, Hansjuergen Agostini ...+3 more authors

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Intravitreal bevacizumab (Avastin®) versus ranibizumab (Lucentis®) for the treatment of age-related macular degeneration: a safety review

Christine Schmucker,* Yoon K Loke,† Christoph Ehlken,‡ Hansjuergen T Agostini,‡ Lutz L Hansen,‡ Gerd Antes,* Monika Lelgemann§

*German Cochrane Centre, University Medical Centre Freiburg, Germany
†School of Medicine, University of East Anglia, Norwich, United Kingdom
‡University Eye Hospital, University Medical Centre Freiburg, Germany
§Health Technology Assessment Centre, University Bremen, Germany

Correspondence to Christine Schmucker, PhD, German Cochrane Centre, Institute of Medical Biometry and Medical Informatics, Department of Medical Biometry and Statistics, University Medical Centre Freiburg, Stefan-Meier-Str. 26, 79104 Freiburg, Germany

E-mail: schmucker@cochrane.de, *Tel:* ++49 (0)761/203-6660, *Fax*++49 (0)761/203-6712

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ABSTRACT

Aim: We conducted a systematic review to compare adverse effects (AE) and the reporting of harm in randomised controlled trials (RCTs) and non-RCTs evaluating intravitreal ranibizumab and bevacizumab in age-related macular degeneration.

Methods: Medline, Embase and the Cochrane Library were searched with no limitations of language and year of publication. We included studies which compared bevacizumab or ranibizumab as monotherapy with any other control group. Case series were included if they met predefined quality standards.

Results: The 2-year results of phase III trials evaluating ranibizumab show that the rates of serious ocular AE were low (≤2.1%) but indicate major safety concerns (Risk ratio (RR) 3.13, 95%-CI 1.10–8.92). We also noted a possible signal with regards to thromboembolic events (RR 1.35, 95%-CI 0.66–2.77) and a significant increase in non-ocular haemorrhage (RR 1.62, 95%-CI 1.03–2.55).

In contrast to ranibizumab trials, the RCTs evaluating bevacizumab are of limited value. The main shortcomings are small sample sizes and an apparent lack of rigorous monitoring for AE. A critical assessment of the large number of published case series evaluating bevacizumab also shows that no reliable conclusions on safety can be drawn using this study design. Therefore, any perception that intravitreal bevacizumab injections are not associated with major ocular or systemic AE are not supported by reliable data.

Conclusion: The bevacizumab studies show too many methodological limitations to rule out any major safety concerns. Higher evidence from ranibizumab trials suggests signals for an increased ocular and systemic vascular and haemorrhagic risk which warrants further investigation.

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people over the age of 50 in the developed world.[1] Although an estimated 80% of patients with AMD have the non-neovascular form,[2] the neovascular (wet or exudative) form is responsible for almost 90% of severe visual loss resulting from AMD.[3]

Anti-angiogenic therapy, e.g., anti-vascular endothelial growth factors (anti-VEGF), which aims to prevent further neovascularization rather than only destroy it, is the latest approach to the treatment of exudative AMD. Currently, the most commonly used VEGF antagonists are ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) and bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA). Ranibizumab, which is an antibody fragment from the bevacizumab molecule with an increased binding affinity for all forms of VEGF, has been approved for the treatment of patients with neovascular AMD by the Food and Drug Administration and by the European Medicines Agency since 2006 and 2007, respectively. The approval was based on three randomised controlled trials (RCTs).[4] Two of these studies showed that approximately 95% of the patients treated with monthly ranibizumab injections lost fewer than 15 letters in 12 months, compared to 64% of patients receiving PDT [5] and 62% receiving sham treatment.[6] In addition, approximately every third patient showed improvements in visual acuity under ranibizumab treatment. The costs of ranibizumab, however, are immense. Using monthly injections with a dose of 0.5 mg, the annual costs come to more than US$ 23,000 per patient.[7]

In contrast to ranibizumab, bevacizumab was not developed for the treatment of AMD and consequently has no approval for this use. Bevacizumab is approved for the treatment of specific cancers, e.g., metastatic colon and rectum cancer. Even before ranibizumab was licensed, bevacizumab had been used as an off-label treatment for AMD. The first report of intravitreal bevacizumab administration for neovascular AMD was published in 2005.[8] After this initial report, numerous case series which (apparently) support the efficacy and safety of bevacizumab were published. The costs of intravitreal bevacizumab are much less than for ranibizumab. Small aliquots in syringes for intraocular injections can be prepared for about US$ 17-50 a month (≤ US$ 600 annually).[7]

Despite lacking evidence, most published reviews agree that bevacizumab seems to be, similar to ranibizumab, effective in maintaining visual acuity. However, the safety and tolerability of bevacizumab in comparison to ranibizumab have not been adequately assessed and hence, the crucial question whether the existing safety data justify the widespread intravitreal off-label use of bevacizumab has not yet been answered. Moreover, it is essential to assess differences in reporting of harm between well-controlled phase III studies, RCTs which do not fulfil phase III study requirements, and non-RCTs. In particular, a critical assessment of the large number of published case series evaluating bevacizumab will show to what extent they can be used as a substitute for high quality trials.

MATERIALS AND METHODS

Systematic literature search

We searched Medline (Ovid), Embase and the Cochrane library from inception until March 2008. An update search focusing on RCTs was carried out in August 2009. The search strategy was based on combinations of medical subject headings (MeSH) and keywords and was not restricted to specific languages or years of publication. The search strategy used in Medline is presented in appendix A. Search strategies for other databases were modified to meet the requirements of each database. The searches were supplemented by handsearching the bibliographies of included studies and reviews and by contacting the pharmaceutical manufacturer (Genentech) of ranibizumab and bevacizumab. Currently conducted RCTs comparing Avastin® versus Lucentis® were searched both in the register for clinical trials (http://clinicaltrials.gov/) and in the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/).

Study selection

Included were RCTs and non-RCTs which compared intravitreal bevacizumab or ranibizumab as monotherapy with any other treatment in patients with neovascular AMD. Case series were included if they enrolled a minimum of ten patients and met predefined quality standards; that is, the publication had to provide adequate information regarding patient selection criteria or the selection of patients had to be consecutive. Studies which included patients with other indications than exudative AMD, patients previously treated with VEGF inhibitors or patients receiving systemic anti-VEGF therapy were excluded.

Data extraction and quality assessment

Titles and abstracts were reviewed using the above mentioned selection criteria. Full papers of appropriate studies were obtained for detailed evaluation. Data extraction and quality assessment was carried out after a modified evaluation tool of the Center for Reviews and Dissemination (Chapter 4, Systematic reviews of adverse effects).[9] Information on the number of participants, ascertainment of exposure (e.g., dosage and frequency of drug administered), follow-up time, definition of expected adverse effects, method used to collect adverse effects data, ascertainment of outcomes (ocular and systemic adverse effects) and transparency of patient flow were abstracted. All stages of study selection, data extraction and quality assessment were done independently by two reviewers (CS and CE *or* CS and ML). Any disagreement was resolved by discussion and consensus.

Statistical analysis

Ranibizumab data were analysed using the R software.[10] This programme was used to compute statistics and generate forest plots to compare safety outcomes in different treatment arms. A chi-square test (p-value < 0.05) and an I^2 test were used to test for statistical heterogeneity between studies. We used the fixed effects model (Mantel-Haeszel method) in the meta-analysis of rare events as it has been shown to be the more appropriate and less biased approach compared to the random effects model.[11] A narrative summary was provided for data that were unsuitable for pooling (studies evaluating bevacizumab).

RESULTS

Results of the search and selection process

The numbers of studies identified at each stage of the systematic review are shown in fig 1. After removing duplicate references, the searches identified 3628 citations. The inclusion criteria were met by four RCTs [6, 12, 19, 20] (11 publications [5, 6, 12-20]) evaluating ranibizumab *vs* PDT, sham or usual care with a total of 1392 patients and four RCTs [21-24] (five publications [21-25]) evaluating bevacizumab *vs* PDT ± triamcinolone with a total of 287 patients. In addition, 17 case series [26-42] examining bevacizumab including a total of 1790 patients were analysed.

Study characteristics

Ranibizumab (RCTs)

Characteristics of the RCTs evaluating intravitreal ranibizumab are presented in table 1a. The ANCHOR study which compared monthly ranibizumab injections with PDT enrolled 423 patients with predominantly classic subfoveal CNV.[12] Follow-up time was 24 months. The MARINA study enrolled 716 patients with minimally classic and occult subfoveal CNV and compared monthly intravitreal ranibizumab with sham injections over 24 months.[6] The PIER study also used sham as a comparator and enrolled 184 patients with occult or classic subfoveal CNV.[19] In contrast to the MARINA study, treated patients received ranibizumab injections once monthly for three consecutive months, followed by a dose administered once every three months (follow-up time: 12 months). Heier 2006 randomised 64 patients to monthly intravitreal ranibizumab with varying doses for three months or usual care (i.e., PDT in predominantly classic lesions and observation in all other lesions).[20] In the second part of the study, patients could continue their regimen for three additional months or cross over to the alternative treatment. All RCTs evaluating ranibizumab were multicenter trials. The ANCHOR,[12] MARINA [6] and PIER [19] study were sponsored by pharmaceutical companies. The source of funding was not reported in the study of Heier 2006.[20]

Bevacizumab (RCTs)

Table 1a shows study characteristics of RCTs evaluating intravitreal bevacizumab. Bashshur 2007 randomised 64 patients with predominantly classic CNV to PDT or intravitreal bevacizumab injections pro re nata.[21] The patients were followed-up for six months. The three months study of Lazic 2007 enrolled 165 patients with minimally classic or occult CNV and compared a single bevacizumab injection with a single PDT session or a combination therapy.[22] Hahn 2007 used PDT in combination with triamcinolone as comparator and enrolled 30 patients with occult or (minimally) classic subfoveal CNV.[23] The patients in this

study received monthly bevacizumab injections for three consecutive months. Saccu 2009 also used PDT in combination with triamcinolone and enrolled 28 patients with occult or (minimally) classic subfoveal CNV.[24] Treated patients received bevacizumab injections once monthly for three consecutive months, followed by a dose administered pro re nata. Follow-up time was 12 months. All trials evaluating bevacizumab were monocenter studies. Two studies reported that no pharmaceutical sponsor was involved,[21, 23] and two did not provide data on the source of funding.[22, 24]

Bevacizumab (case series)

In total 11 prospective [26-36] and six retrospective [37-42] case series evaluating bevacizumab were analysed (table 1b). The number of included patients ranged between 13 and 625 (median: 48). Minimum follow-up time was one month and maximum follow-up 12 months. The Patients received between one and four injections and the applied dosage of bevacizumab varied between 1.0 mg and 2.5 mg. In ten case series [27, 30, 33, 35, 36, 38-42] patients were injected pro re nata, in three case series [26, 31, 37] a single injection of bevacizumab was given and in four case series [28, 29, 32, 34] injections at intervals of four or six weeks were administered. Funding sources were specified in nine publications.[29-31, 33-35, 38, 39, 41] A pharmaceutical sponsor was, however, not reported.

Table 1a Characteristics of *RCTs* evaluating ranibizumab and bevacizumab

	No included patients	**No anti-VEGF treated patients**	**Follow-up [months]**	**Dosage [mg]**	**No injections/ patient [mean]**	**Sponsor**
Ranibizumab ANCHOR 2009 [12]	423	280	24	0.3 / 0.5 monthly	24	pharmaceutical industry
Ranibizumab MARINA 2006 [6]	716	478	24	0.3 / 0.5 monthly	21	pharmaceutical industry
Ranibizumab PIER 2008 [19]	184	121	12	0.3 / 0.5 3 monthly, then every 3 mos	10	pharmaceutical industry
Ranibizumab Heier 2006 [20]	69	53	7	0.3 / 0.5*	8	not specified
Bevacizumab Bashshur 2007 [21]	64	32	6	2.5 pro re nata	2.4	no
Bevacizumab Lazic 2007 [22]	165	55	3	1.25 single injection	1	not specified
Bevacizumab Hahn 2007 [23]	30	10	3	1.0 monthly	3	no
Bevacizumab Sacu 2009 [24]	28	14	12	1.0 3 monthly, then pro re nata	6.8	not specified

*Four monthly injections *or 1* injection of 0.3 mg followed by 3 monthly injections of 0.5 mg; after 3 months: cross over design.

Table 1b Characteristics of *case series* evaluating bevacizumab

	No included patients	Follow-up [months]	Dosage [mg]	No injections/ patient [mean]	Sponsor
Prospective case series					
Abraham-Marin 2007 [26]	39	1	2.5 single injection	1	not specified
Aisenbrey 2007 [27]	30	3	1.25 pro re nata	1.6	not specified
Bashshur 2006 [28]	17	3	2.5 monthly	3	not specified
Bashshur 2008 [29]	60	12	2.5 3 monthly, then pro re nata	3.4	yes, but no pharmaceutical industry
Chen 2007 [30]	102	1.5-6.5	1.25 pro re nata	0.5 per months	no
Costa 2006 [31]	45	3	1.0, 1.5, 2.0* single injection	1	no
Falkenstein 2007 [32]	18†	6	1.25 every 6 weeks	3.6	not specified
Geitzenauer 2006 [33]	13	3	1.0 pro re nata	3	yes, but no pharmaceutical sponsor
Giansanti 2007 [34]	27	6	1.25 3 monthly	3	yes, but no pharmaceutical sponsor
Lazic 2007a [35]	102	1.5-6	1.25 pro re nata	1-4	no
Lazic 2007b [36]	48	1.5-6	1.25 pro re nata	nr	not specified
Retrospective case series					
Arias 2007 [37]	40	≥6	1.25 single injection	1	not specified
Cleary 2008 [38]	111‡	1-12	1.25 pro re nata	1.7	no
Goverdhan 2008 [39]	53	2-12	1.25 pro re nata	1.4	no
Jonas 2007 [40]	625	≥1	1.5 pro re nata	1.1	not specified
Madhusudhana 2007 [41]	115	4.6	1.25 pro re nata	1.9	no
Wu 2008 [42]	345§	12	1.25 or 2.5‖ pro re nata	3.3	not specified

*Approximately 33% of patients received 1.0 mg, 33% received 1.5 mg and 33% received 2.5 mg intravitreal bevacizumab.
†The study evaluated a 2nd cohort including 20 patients receiving bevacizumab+pegaptanib. This cohort is not considered in the review.
‡Data of 111 patients presented, therefrom 72 with exudative AMD.
§Data of 1173 patients presented, therefrom 345 with exudative AMD.
‖Approximately 16% of patients received 1.25 mg and 84% of patients received 2.5 mg intravitreal bevacizumab.

Ocular adverse effects

Ranibizumab (RCTs)

Intravitreal ranibizumab injections have been associated with *endophthalmitis (≤2.1%), uveitis (≤1.3%), retinal detachment (≤1.5%), retinal tear (≤1.9%), vitreous haemorrhage (≤8.0%)* and *traumatic lens damage (≤0.4%)* (table 2a).[6, 12, 20] A pooled analysis on serious ocular adverse effects indicated some major safety issues (Risk ratio [RR] 3.13, p=0.03, fig 2a). In addition, all trials reported a transient increase in *intraocular pressure* in the study eye after intravitreal injections.

Bevacizumab (RCTs)

Most RCTs evaluating bevacizumab stated generically that ocular adverse effects were not noted. As the studies did not provide a detailed breakdown on the presence or absence of specific adverse effects, we are left to make the assumption that intravitreal bevacizumab injections were not associated with major problems, such as *endophthalmitis, uveitis, retinal detachment, lens damage and vitreous haemorrhage* (table 2a). Any transient increase in *intraocular pressure* after the injections was also not reported. However, an increased rate of *pigment epithelial tears* (5.5% *vs* 0.0%), *posterior vitreous detachment* (14.6% *vs* 0.0%) and *cataract progression* (7.3% *vs* 0.0%) was reported in one RCT evaluating bevacizumab.[22]

Bevacizumab (case series)

Four publications reported an increased rate of *endophthalmitis* (range between 0.2% and 0.9%, table 2b).[38, 40, 41, 42] An increased rate of *retinal pigment epithelial tears (rips)* was observed in five reports (range between 0.9% and 7.5%).[34, 35, 37, 38, 41] *Vitreous detachment* was reported in 9.8% of patients in one publication [35] and an increased rate of *submacular haemorrhage* was observed in two case series (2.7% [38], 7.5% [39]). Moreover, in the retrospective case series of Wu 2008 an increased rate of *uveitis* (0.3%), *retinal detachment* (0.6%) and *vitreous haemorrhage* (0.08%) was reported.[42] Six case series reported minor ocular adverse effects, such as *pain*,[31] *conjunctival hyperemia*,[31] *subconjunctival haemorrhage*,[26, 31, 32, 42] *mild intraocular inflammation*,[26] *transient corneal epitheliopathy* [34] and *transient blurred vision*.[35]

Table 2a Rates of *ocular adverse effects* under ranibizumab and bevacizumab / *RCTs*

	Endophthalmitis (%)			**Uveitis (%)**			**Retinal detachment (%)**			**Retinal tear (%)**			**Lens damage (traumatic) (%)**			**Vitreous haemorrhage (%)**		
Ranibizumab ANCHOR 2009 [12]	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT
	0.0	**2.1**	0.0	**0.0**	**0.7**	0.0	**1.5**	**0.0**	0.7	**0.0**	**0.7**	0.0	**0.0**	**0.0**	0.0	**1.5**	**0.0**	0.0
Ranibizumab MARINA 2006 [6]			Sham			Sham			Sham			Sham			Sham			Sham
	0.8	**1.3**	0.0	**1.3**	**1.3**	0.0	**0.0**	**0.0**	0.4	**0.4**	**0.4**	0.0	**0.0**	**0.4**	0.0	**0.4**	**0.4**	0.8
Ranibizumab PIER 2008 [19]	**0.0**	**0.0**	0.0	**0.0**	**0.0**	0.0	**0.0**	**0.0**	0.0	**0.0**	**0.0**	0.0	**0.0**	**0.0**	0.0	**0.0**	**0.0**	0.0
Ranibizumab Heier 2006 [20]	0.3/0.5mg		UC			UC			UC	0.3/0.5		UC			UC			UC
	1.6*		0.0	**0.0**	**0.0**	0.0	**0.0**	**0.0**	0.0	**1.9***		0.0	**nr**	**nr**	nr	**8.0**	**3.6**	0.0
Bevacizumab Bashshur 2007 [21]	2.5mg		PDT	2.5mg		PDT	2.5mg		PDT	2.5mg		PDT	2.5mg		PDT	2.5mg		PDT
	nr		nr	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr
Bevacizumab Lazic 2007 [22]	1.25mg		PDT	1.25mg		PDT	1.25mg		PDT	1.25mg		PDT	1.25mg		PDT	1.25mg		PDT
	nr		nr	**nr**		nr	**nr**		nr	**5.5**		0.0	**nr**		nr	**nr**		nr
Bevacizumab Hahn 2007 [23]	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC
	nr		nr	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr
Bevacizumab Sacu 2009 [24]	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC
	0.0		0.0	**0.0**		0.0	**0.0**		0.0	**nr**		nr	**0**		0	**nr**		nr

Nr, not reported; UC, usual care; IvTC, intravitreal triamcinolone.
*After 3 months (part I of the study).

Table 2b Rates of *ocular adverse effects* under bevacizumab / *case series*

	Endoph-thalmitis (%)	Uveitis (%)	Retinal detachment (%)	Retinal tear (%)	Lens damage (%)	Vitreous haemorrhage (%)	Other ocular adverse effects
Prospective case series							
Abraham-Marin 2007 [26]	nr	nr	nr	nr	nr	nr	Subconjunctival haemorrhage 7.7%, mild inflammation 20.5%
Aisenbrey 2007 [27]	0.0	0.0	nr	nr	nr	nr	
Bashshur 2006 [28]	nr	nr	nr	nr	nr	nr	
Bashshur 2008 [29]	nr	nr	nr	nr	nr	nr	
Chen 2007 [30]	0.0	0.0	nr	nr	nr	nr	
Costa 2006 [31]	0.0	0.0	nr	nr	0.0	nr	Pain 18%, conjunctival hyperemia 38%, subconjunctival haemorrhage 38%
Falkenstein 2007 [32]	0.0	0.0	0.0	0.0	nr	nr	Subconjunctival haemorrhage (rare)
Geitzenauer 2006 [33]	nr	nr	nr	nr	nr	nr	
Giansanti 2007 [34]	0.0	nr	0.0	7.4	nr	0.0	Transient corneal epitheliopathy 7.4%
Lazic 2007a [35]	nr	nr	present*	2.0	0.0	nr	Vitreous detachment 9.8%, transient blurred vision
Lazic 2007b [36]	nr	nr	nr	nr	0.0	nr	
Retrospective case series							
Arias 2007 [37]	nr	nr	nr	7.5 (study goal)	nr	nr	
Cleary 2008 [38]	0.9	0.0	nr	2.7	nr	nr	Submacular haemorrhage 2.7%
Goverdhan 2008 [39]	nr	nr	nr	nr	nr	nr	Submacular haemorrhage 7.5% (study goal)
Jonas 2007 [40]	0.2 (study goal)	nr	nr	nr	nr	nr	
Madhusudhana 2007 [41]	0.9	nr	nr	0.9	nr	nr	
Wu 2008† [42]	0.60	0.3	0.6 (tractional)	nr	nr	0.08	Subconjunctival haemorrhage 71.4%, IOP increase 0.6%, transient hypotony 0.08%

Nr, not reported; RPE, retinale pigment epithelium.
*Number not given.
†1265 patients injected, 92 lost to follow-up, data of 1173 patients presented , therefrom 345 with exudative AMD. The given percentage rates refer to 1173 patients.

Nonocular adverse effects

Ranibizumab (RCTs)

The rate of nonocular adverse effects of single RCTs are displayed in table 3a and pooled analysis for different systemic outcomes in fig 2b, 2c and 2d. The rate of *key arterial nonfatal thromboembolic effects (myocardial infarction and stroke)* during the first and second year of the ANCHOR [12] and MARINA [6] trials was numerically, but not statistically significantly higher in the 0.5 mg arm than in the control arm (3.6% [12] and 2.5%,[6] respectively *vs* 1.4% and 0.8%, respectively). However, a pooled analysis indicated that there may be a safety signal (RR 1.35, 95%-CI 0.66-2.77). In the ANCHOR,[12] MARINA [6] and PIER [19] study, the incidence of *serious nonocular haemorrhage (such as gastrointestinal haemorrhage, traumatic subdural haematoma and duodenal ulcer haemorrhage)* was also consistently higher in the ranibizumab than in the control groups (2.9% [0.3 mg] [12], 2.1% [0.5 mg] [6] and 0.6% [0.5 mg] [19] *vs* 0.7%, 0.8% and 0.0%). A pooled analysis indicated that this risk reached the standard thresholds for statistical significance (RR 1.62, p=0.04). *Treatment-emergent hypertension* was not more common in the ranibizumab than in the control groups.[6, 12, 19] In the safety study of Heier 2006 nonocular adverse effects were not specified.[20] However, it was reported that the only nonocular adverse event judged by an investigator to be a possible effect of ranibizumab was a case of metallic taste in the mouth.

Bevacizumab (RCTs)

Intravitreal bevacizumab injections were apparently not associated with any systemic adverse effects in the existing RCTs (table 3a). This assumption is based on the following limited details concerning the harms reported within the articles: Two trials mentioned generically that no systemic effects were observed.[21, 24] One study did not mention systemic complications in the results.[23] Another study reported that no thromboembolic events were observed.[22] Other nonocular complications were not mentioned in this study.

Bevacizumab (case series)

Nonocular adverse effects were observed in one retrospective case series (table 3b).[42] The incidence of *cerebrovascular accidents* and *myocardial infarct* was 0.3% and the incidence of *acute hypertension* was 1.5%. In addition, 0.6% of patients with exudative AMD showed an *iliac artery aneurysm*. Overall, eight case series mentioned - by using numerical data - that no thromboembolic events occurred.[28-30, 34-36, 38, 41] Six publications stated briefly that no systemic adverse effects were observed (except blood pressure was reported in more detail) [26, 27, 31-33, 39] and two publications did not mention systemic complications.[37, 40] However, the primary study goal of these two case series were ocular complications.

Table 3a Rates of *systemic adverse effects* under ranibizumab and bevacizumab / *RCTs*

	Death (%)			**Myocardial infarction (nonfatal) (%)**			**Cerebrovascular accident (nonfatal) (%)**			**Nonocular haemorrhage (%)**			**(Treatment-emergent) hypertension (%)**		
	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT	0.3mg	0.5mg	PDT
Ranibizumab ANCHOR 2009 [12]	**3.7**	**2.1**	3.5	**0.7**	**3.6**	1.4	**2.2**	**0.0**	1.4	**8.8*** **2.9†**	**9.3*** **2.1†**	4.9* 0.7†	**9.5**	**12.1**	16.1
			Sham			Sham			Sham			Sham			Sham
Ranibizumab MARINA 2006 [6]	**2.1**	**2.5**	2.5	**2.5**	**1.3**	1.7	**1.3**	**2.5**	0.8	**9.2*** **1.3†**	**8.8*** **2.1†**	5.5* 0.8†	**17.2‡**	**16.3‡**	16.1‡
Ranibizumab PIER 2008 [19]	**0.0**	**0.0**	0.0	**0.0**	**0.0**	0.0	**0.0**	**0.0**	0.0	**3.4*** **0.0†**	**6.6*** **0.6†**	4.8* 0.0†	**6.8**	**9.8**	8.1
			UC			UC			UC			UC			UC
Ranibizumab Heier 2006 [20]	**nr**	**nr**	nr	**nr**	**nr**	nr	**nr**	**nr**	nr	**nr**	**nr**	nr	**nr**	**nr**	nr
	2.5mg		PDT	2.5mg		PDT	2.5mg		PDT	2.5mg		PDT	2.5mg		PDT
Bevacizumab Bashshur 2007 [21]	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr	**0.0**		0.0
	1.25mg		PDT	1.25mg		PDT	1.25mg		PDT	1.25mg		PDT	1.25mg		PDT
Bevacizumab Lazic 2007 [22]	**nr**		nr	**0**		0	**0**		0	**nr**		nr	**nr**		nr
	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC
Bevacizumab Hahn 2007 [23]	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr
	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC	1.0mg		PDT+ivTC
Bevacizumab Sacu 2009 [24]	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr	**nr**		nr

Nr, not reported; IvTC, intravitreal triamcinolone.
*Refers to serious or nonserious nonocular haemorrhage.
†Refers to serious nonocular haemorrhage.
‡ Investigator defined hypertension.

Table 3b Rates of *systemic adverse effects* under bevacizumab / *case series*

	Death (%)	Myocardial infarction (%)	Cerebrovascular accident (%)	Nonocular haemorrhage (%)	(Treatment-emergent) hypertension (%)	Other systemic adverse effects
Prospective case series						
Abraham-Marin 2007 [26]	nr	nr	nr	nr	nr	nr
Aisenbrey 2007 [27]	nr	nr	nr	nr	0.0	nr
Bashshur 2006 [28]	0.0	0.0	0.0	nr	0.0	nr
Bashshur 2008 [29]	0.0	0.0	0.0	nr	0.0	nr
Chen 2007 [30]	nr	0.0	nr	nr	nr	nr
Costa 2006 [31]	nr	nr	nr	nr	0.0	nr
Falkenstein 2007 [32]	nr	nr	nr	nr	nr	nr
Geitzenauer 2006 [33]	nr	nr	nr	nr	0.0	nr
Giansanti 2007 [34]	0.0	0.0	0.0	nr	0.0	nr
Lazic 2007a [35]	nr	0	0	nr	nr	nr
Lazic 2007b [36]	nr	0	0	nr	nr	nr
Retrospective case series						
Arias 2007 [37]	nr	nr	nr	nr	nr	nr
Cleary 2008 [38]	0.0	0.0	0.0	nr	0.0	nr
Goverdhan 2008 [39]	nr	nr	nr	nr	nr	nr
Jonas 2007 [40]	nr	nr	nr	nr	nr	nr
Madhusudhana 2007 [41]	0.0	0.0	0.0	0.0	0.0	nr
Wu 2008* [42]	0	0.29	0.29	nr	1.45	Iliac artery aneurysm 0.58%

Nr, not reported.
*1265 patients injected, 92 lost to follow-up, data of 1173 patients presented, therefrom 345 with exudative AMD. The given percentage rates refer to 345 patients with AMD.

Methodological limitations

RCTs

The methodological quality of RCTs evaluating ranibizumab and bevacizumab is presented in table 4a. In contrast to the pharmaceutical industry sponsored RCTs evaluating ranibizumab, the results of the RCTs evaluating bevacizumab are of limited value. The main limitations stemmed from the lack of any description as to how adverse effects were rigorously monitored, as well as the inadequate reporting of actual events. For example, none of the RCTs evaluating bevacizumab defined the method used to collect adverse effects data sufficiently or provided an adequate definition of expected adverse effects. In addition, in two of four RCTs evaluating bevacizumab the follow-up time was not sufficient to assess potential negative systemic effects, such as death or thromboembolic events (less than six months).[22, 23] In contrast, RCTs evaluating ranibizumab showed follow-up times of up to 24 months.[6, 12] Beside the above mentioned shortcomings, the sample size for bevacizumab treated patients was much lower than for ranibizumab treated patients (112 *vs* 941) and the number of received injections differed greatly (bevacizumab: between one and seven intravitreal injections per patient, ranibizumab: up to 24 injections per patient).

Case series

A critical assessment of the large number of published case series showed that no reliable conclusions on safety can be drawn using this study design (table 4b). For example, of 11 prospective case series including 501 patients, only two evaluated more than 100 patients.[30, 35] However, the lost to follow-up was between 60% and 70% and reasons for drop-outs were not given in these publications. In addition, more than half of the evaluated case series did not describe if all of the originally included patients were considered in the results (transparency of patient flow not given).[26, 28, 30, 34, 35, 37-41] Similar to RCTs evaluating bevacizumab, only four [31, 37, 39, 40] of 17 case series provided a definition of expected adverse effects and three [27, 39, 41] (partly) defined the method used to collect adverse effects data. The currently available safety data from case series are - similar to the data from RCTs - further limited by the low number of received bevacizumab injections and short follow-up times.

Table 4a Methodological quality of *RCTs* evaluating ranibizumab and bevacizumab

	Follow-up time sufficient to assess safety*	Definition of expected AE	Definition of method used to collect AE data	Transparency of patient flow	Validity safety
Ranibizumab ANCHOR 2009 [12]	yes	yes†	yes‡	yes	high
Ranibizumab MARINA 2006 [6]	yes	yes§	yes‖	yes	high
Ranibizumab PIER 2008 [19]	yes	yes#	yes**	yes	high
Ranibizumab Heier 2006 [20]	yes	in part††	no	yes	moderate
Bevacizumab Bashshur 2007 [21]	yes	in part‡‡	in part§§	yes	low
Bevacizumab Lazic 2007 [22]	no	no	no	yes	low
Bevacizumab Hahn 2007 [23]	no	no	no	unclear	low
Bevacizumab Sacu 2009 [24]	yes	no	no	yes	low

AE, adverse effects.
*This parameter addresses "long-term" harm, such as fatal or nonfatal systemic complications (e.g., stroke or myocardial infarction). We considered follow-up times of <6 months as not sufficient to assess these complications.
†For serious ocular AE and grading scales for intraocular inflammation see tables 2, 3 and 6 of the supplementary study appendix.
‡Safety assessments included: intraocular pressure measurement (before and 60±10 min after each study treatment), indirect ophthalmoscopy, slit lamp examination, assessment of the incidence and severity of ocular and nonocular AE, changes and abnormalities in clinical laboratory parameters and vital signs, immunoreactivity to ranibizumab. Independent data monitoring committee met regularly one or more times a year during the study to review unmasked safety summaries prepared by an external statistical coordinating center.
§For serious ocular AE and grading scales see tables 3-5 of the supplementary study appendix.
‖After injection, patients remained in the clinic at least 60 minutes for safety monitoring and measurement of intraocular pressure. Site personnel contacted patients 2±1 days postinjection to elicit reports of any new ocular symptoms. Patients were evaluated 7 days after their first ranibizumab or sham injection, but they did not return 7 days after subsequent injections. Indirect ophthalmoscopy, intraocular pressure measurement, VA testing, and slit lamp examination were performed by the evaluating physician before every monthly study treatment. Safety outcomes included: incidence and severity of ocular and nonocular AE changes, abnormalities in clinical laboratory parameters and vital signs, assessment of immunoreactivity to ranibizumab. During the study, an independent data monitoring committee met twice per year to review unmasked safety summaries prepared by an external statistical coordinating center.
#Grading scales for flare/cells and vitreous hemorrhage density were used to grade intraocular inflammation or vitreous hemorrhage, assessed by slit-lamp examination, see supplemental study tables B1 to B3.
**Key safety assessments: incidence and severity of ocular and nonocular AE, changes in vital signs and the incidence of positive serum antibodies to ranibizumab. Slit-lamp examination and indirect ophthalmoscopy were performed before each study injection. IOP was measured using applanation tonometry before and 60±10 minutes after each study treatment.
††Verbatim descriptions of all AE were converted to medical dictionary for regulatory activities terms for statistical analysis. Inflammation was evaluated by grading flare and cells from 0-4+.
‡‡Patients were observed for any systemic thromboembolic events or ocular complications.
§§All patients in the bevacizumab group had blood pressure measurements at every visit. Complete blood count and urinary analysis were taken at baseline and 1 week after any injection.

Table 4b Methodological quality of *case series* evaluating bevacizumab

	Follow-up time sufficient to assess safety*	Definition of expected AE	Definition of method used to collect AE data	Transparency of patient flow	Validity safety
Prospective case series					
Abraham-Marin 2007 [26]	no	no	no	unclear	low
Aisenbrey 2007 [27]	no	no	in part	yes	low
Bashshur 2006 [28]	no	no	no	unclear	low
Bashshur 2008 [29]	yes	no	no	yes	low
Chen 2007 [30]	yes	no	no	no	low
Costa 2006 [31]	no	yes	no	yes	low
Falkenstein 2007 [32]	yes	no	no	yes	low
Geitzenauer 2006 [33]	no	no	no	yes	low
Giansanti 2007 [34]	yes	no	no	unclear	low
Lazic 2007a [35]	yes	no	no	no	low
Lazic 2007b [36]	no	no	no	yes	low
Retrospective case series					
Arias 2007 [37]	yes	yes	no	unclear	low
Cleary 2008 [38]	yes	no	no	no	low
Goverdhan 2008 [39]	not applicable	yes	yes	unclear	moderate
Jonas 2007 [40]	not applicable	yes	no	unclear	low
Madhusudhana 2007 [41]	no	no	in part	unclear	low
Wu 2008 [42]	yes	no	no	yes	low

*This parameter addresses “long-term” harm, such as fatal or nonfatal systemic complications (e.g., stroke or myocardial infarction). We considered follow-up times of <6 months as not sufficient to assess these complications.

DISCUSSION

Principal findings

Our review indicates that funding may not be a major cause of bias in the reporting of safety data.[43] For example, most RCTs evaluating ranibizumab have been sponsored by the pharmaceutical industry, but they fulfil most of the criteria of reporting adverse effects. The study results of ranibizumab show a potential risk of serious adverse effects related to the injection procedure. In addition, the pooled RR indicates a possible risk of arterial thromboembolic and nonocular haemorrhagic events following intravitreal use of ranibizumab. Since the trials were not powered to detect small differences in adverse event rates, no conclusion can be drawn regarding whether these differences were drug-related or due to chance alone. Therefore, these signals should be investigated in larger epidemiological studies. Despite adequate reporting of adverse effects in RCTs evaluating ranibizumab, uncertainties remain in pharmaceutical industry sponsored trials about the interpretation and conclusions of these effects by the authors.[43] In addition, very rarely adverse effects could not be evaluated in the ranibizumab trials because the number of patients was still too small.

In contrast to the RCTs evaluating ranibizumab, the trials evaluating bevacizumab were not sponsored by the pharmaceutical industry. However, they show - as described above - common methodological weaknesses (e.g., short follow-up times, small sample sizes, and an inadequate reporting of adverse effects). Thus, the findings that intravitreal bevacizumab injections are not associated with major ocular or systemic adverse effects are not supported by reliable data from RCTs.

Beside RCTs, numerous case series evaluating bevacizumab have been published. Not surprisingly, they show major methodological weaknesses and are of limited validity. For example, the often cited retrospective multicenter PACORES study,[42] which is the only publication that provides information on the rates of systemic adverse effects of intravitreal bevacizumab, reports “self-reported” harm data. This can lead, as also discussed by the study authors, to an underestimation of adverse effects. Some case series showed a high lost to follow-up without giving reasons for drop-outs.[e.g., 30, 35] However, a complete follow-up is necessary in order to determine if those patients who withdrew due to adverse effects are different from those who did not adhere. Taking also into account that intravenous bevacizumab for the management of colorectal cancer is associated with major systemic adverse effects, the low (or zero) rates for intravitreal bevacizumab are questionable - even though the dose of intravitreal bevacizumab is about 0.25% of that used for intravenous treatment.

Strengths and weaknesses of this review

Both RCTs and non-RCTs (in particularly case series) were considered for the current review. We were interested in data from non-RCTs, because it is assumed that safety data from this study type are more reliable than data from RCTs.[44] For example, in RCTs, data on adverse effects could be underestimated mainly due to the inclusion of highly selected (non-representative) patients and/or publication bias.[45] In addition, small sample sizes limit the ability to detect rare but serious adverse effects.[45] In contrast, non-RCTs often utilize large database, therefore, it is more likely that rare adverse effects for a wide range of patients can be detected with this study type.[45] However, the current literature shows that in the case of bevacizumab in AMD, no well-conducted non-RCTs with large sample sizes are published.

Other reviews

Up to now, ranibizumab and bevacizumab has been evaluated in several systematic reviews. However, the published reviews focused on the beneficial effect or clinical effectiveness of VEGF inhibitors without adequately addressing adverse effects.[46-48] The reason behind is that due to an ongoing methodological debate about the assessment of adverse effects the conclusions on safety are more complicated and need a very thoroughly and often time-consuming evaluation. However, it is obvious that the inadequacies of the bevacizumab safety data may potentially lead to situations where bevacizumab is used inappropriately or where patients are not fully informed of possible harm and potentially avoidable adverse consequences [49] - in contrast to the clear safety information that is available with the licensed substance which has been evaluated in Phase III trials.

Implications for clinical practice

This review highlights that the perceived low rates of adverse effects for bevacizumab are not supported by reliable data. The published RCTs and case series evaluating bevacizumab are of limited value and, therefore, they can not be used as substitutes for high-quality trials. In addition, higher evidence from ranibizumab trials suggests signals for an increased ocular and systemic vascular and haemorrhagic risk which warrants further investigation.

Results of ongoing head-to-head studies such as the IVAN study in Great Britain and the CATT study in the USA are in progress. Besides evaluating efficacy, these studies should have enough power to address major safety issues of bevacizumab compared to ranibizumab. Initial study results are expected to be available by 2011. In the meantime, patients and doctors should be aware of the insufficient safety data regarding intravitreal bevacizumab.

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None.

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Figure 1 Flow diagram

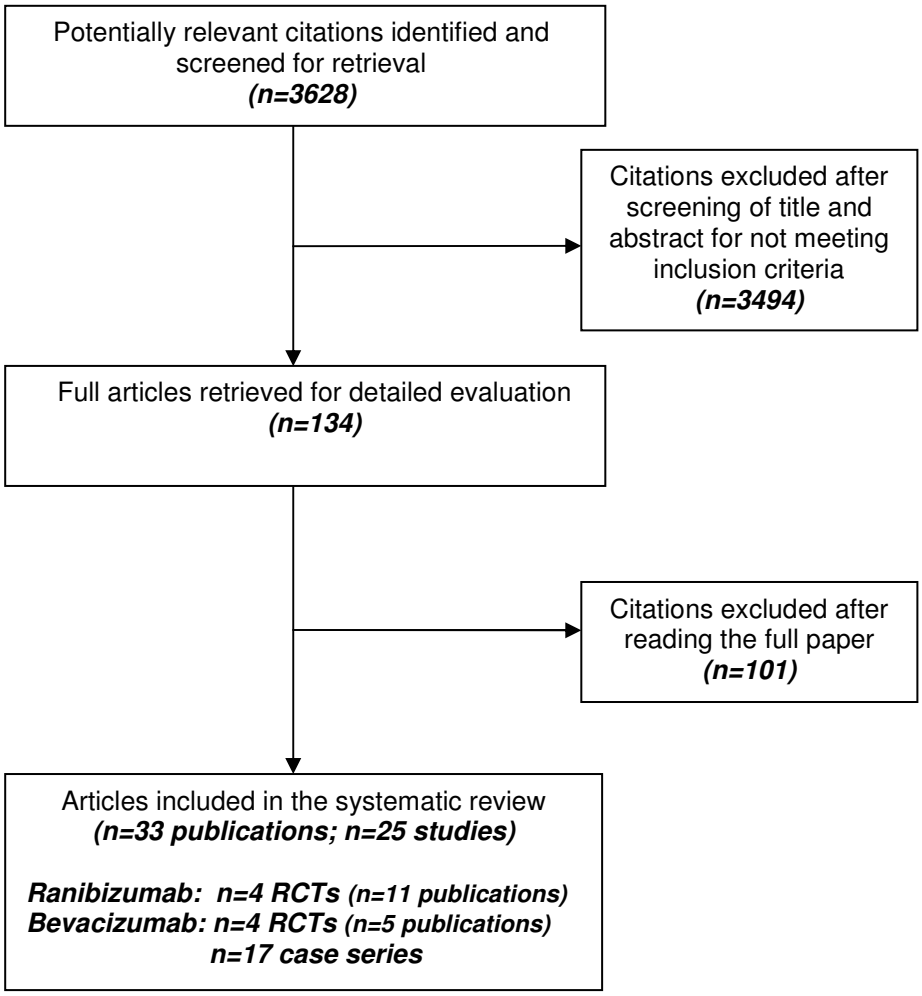
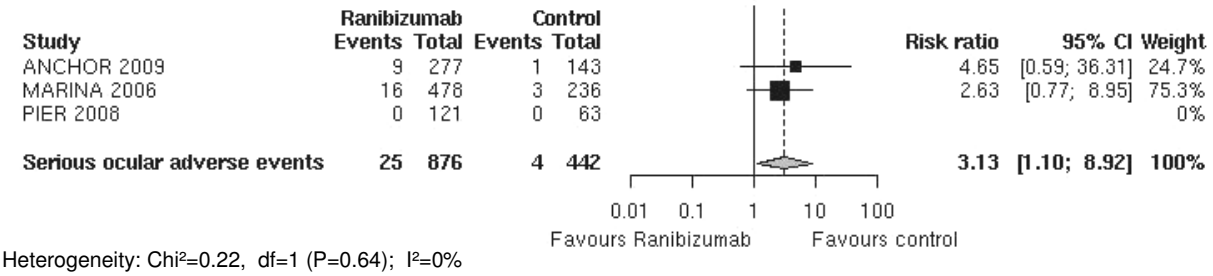


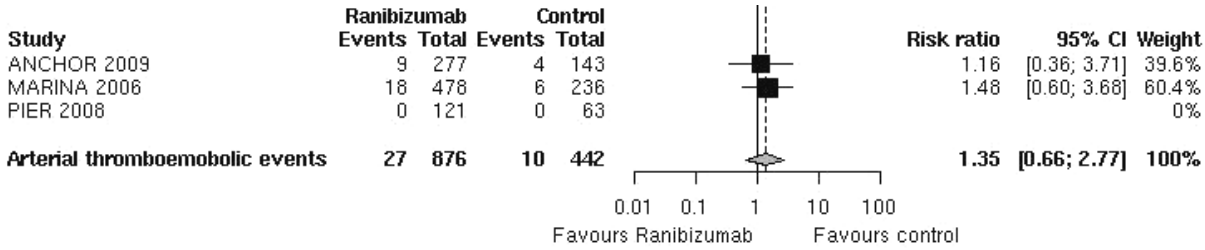
Figure 2 Forest plots of ranibizumab (any dose *vs* any control) for different safety outcomes

a) Serious ocular adverse effects (endophthalmitis, uveitis, retinal detachment, retinal tear, vitreous haemorrhage, traumatic lens damage)



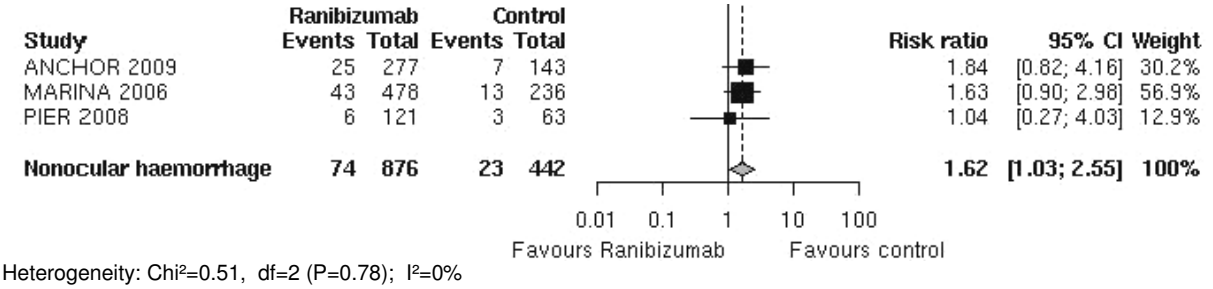
Heterogeneity: Chi²=0.22, df=1 (P=0.64); I²=0%
Test for overall effect: Z=2.13, (P=0.03)
Fixed effect model (Mantel-Haeszel method): RR=3.13, 95%-CI=1.10-8.92

b) Arterial thromboembolic events nonfatal (myocardial infarction, stroke)



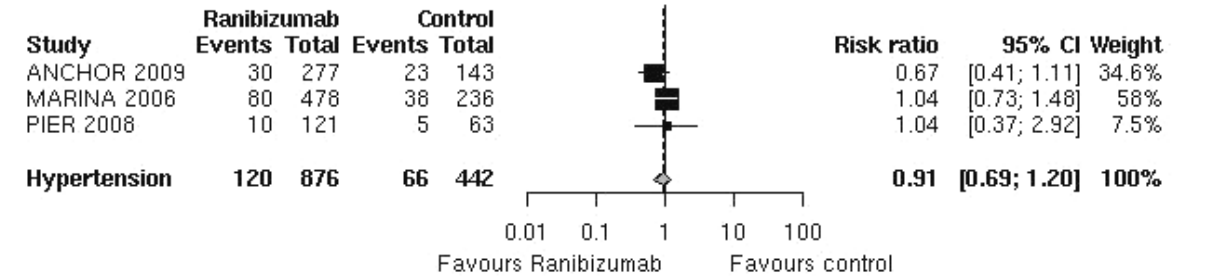
Heterogeneity: Chi²=0.1, df=1 (P=0.75); I²=0%
Test for overall effect: Z=0.83, (P=0.41)
Fixed effect model (Mantel-Haeszel method): RR=1.35, 95%-CI=0.66-2.77

c) Nonocular haemorrhage (serious and nonserious)



Heterogeneity: Chi²=0.51, df=2 (P=0.78); I²=0%
Test for overall effect: Z=2.08, (P=0.04)
Fixed effect model (Mantel-Haeszel method): RR=1.62, 95%-CI=1.03-2.55

d) Hypertension



Heterogeneity: Chi²=1.98, df=2 (P=0.37); I²=0%
Test for overall effect: Z=-0.64, (P=0.52)
Fixed effect model (Mantel-Haeszel method): RR=0.91, 95%-CI=0.69-1.20

Appendix A Search strategy in Medline (Ovid)

#	Searches	Results
1	exp Macular Degeneration/	8909
2	exp Retinal Degeneration/	19448
3	exp neovascularization, pathologic/	23310
4	exp eye/	235449
5	exp eye diseases/	341820
6	exp ophthalmology/	14674
7	4 or 5 or 6	478892
8	3 and 7	6336
9	exp retinal neovascularization/	1334
10	exp Choroidal Neovascularization/	2078
11	exp choroid/ [blood supply]	7896
12	exp Macula Lutea/	7688
13	((macul* or retina* or choroid*) adj5 degener*).tw.	11098
14	((macul* or retina* or choroid*) adj5 neovasc*).tw.	4532
15	((macul* or retina* or choroid*) adj5 neo-vasc*).tw.	6
16	maculopath*.tw.	2006
17	(macul* adj2 lutea).tw.	88
18	amd.tw.	2942
19	cnv.tw.	2083
20	(subfoveal neovasc* or subfoveal neo-vasc*).tw.	178
21	(extrafoveal neovasc* or extrafoveal neo-vasc*).tw.	8
22	(juxtafoveal neovasc* or juxtafoveal neo-vasc*).tw.	8
23	(occult neovasc* or occult neo-vasc*).tw.	27
24	(classic neovasc* or classic neo-vasc*).tw.	12
25	(chor* neovas* or chor* neo-vas*).ot.	44
26	1 or 2 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	41179
27	exp Antibodies, Monoclonal/	135039
28	monoclonal antibod*.mp.	134118
29	exp Angiogenesis Inhibitors/	27451
30	angiogenesis inhibit*.mp.	7033
31	exp Endothelial Growth Factors/	7888
32	((endothelial adj3 growth factor*) or ECDGF or endo-GF).mp.	24508
33	exp Vascular Endothelial Growth Factors/	17886
34	vegf.mp.	17009
35	bevacizumab.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	1417
36	avastin.mp.	289
37	ranibizumab.mp.	142
38	rhufab.tw.	4
39	lucentis.mp.	34
40	pegaptanib.mp.	171
41	macugen.mp.	45

42 or/27-41	236411
43 26 and 42	1893
44 exp animals/	13541475
45 exp humans/	10254739
46 44 not (44 and 45)	3286736
47 43 not 46	1406
48 remove duplicates from 47	1379