OPEN ACCESS

What is the evidence for systemic effects of intravitreal anti-VEGF agents, and should we be concerned?

Robert L Avery

Correspondence to
Dr Robert L Avery, California Retina Consultants, 515 E. Micheltorena St., Ste. C, Santa Barbara, CA 93103, USA; Avery1@jhu.edu

Presented in part at the Retina Physician Symposium, Las Vegas, 7 June 2013.

Received 4 October 2013
Revised 12 November 2013
Accepted 17 November 2013
Published Online First 10 December 2013

ABSTRACT

Anti-vascular endothelial growth factor (VEGF) therapy has revolutionised the treatment of retinal disease, and appears to be very safe. Nevertheless, there are several lines of evidence that imply that small doses of these agents could potentially have a systemic effect. The clinical significance of these systemic effects remains unclear, but further study is indicated.

As an earlier adopter of off-label bevacizumab for retinal disease, I saw firsthand what a great improvement this class of agents offered over our previous treatments. However, as bevacizumab had not been through the usual FDA approval process for intravitreal use, I was vigilant in looking for signs of systemic effects. In 2006, I reported several patients with proliferative diabetic retinopathy (PDR) who exhibited changes in the fellow eye a week after bevacizumab injection.[1] If these observations were actually due to the small amount of drug released into the systemic circulation, I reasoned that we must have been using much higher doses than needed to inhibit retinal neovascularisation in the injected eye. Hence, I reduced the injected dose of bevacizumab down by 200-fold to 6.25 μg and was still able to see an effect on leakage of neovascularisation in the injected eye.[1] Although many fellow eye cases have now been reported, and I have observed it with ranibizumab, aflibercept and bevacizumab, most clinicians have not seen fellow eye effects and discount the plausibility that they occur.[2 3]

Other evidence of systemic effects includes numerous reports of decreased systemic vascular endothelial growth factor (VEGF) levels following intravitreal anti-VEGF injections. Matsuyama *et al* reported a marked reduction in plasma VEGF levels 1 day, 1 week and 1 month after bevacizumab injection in patients with severe PDR, most of whom had rubeosis.[4] Carneiro *et al* compared the effects of intravitreal bevacizumab and ranibizumab on plasma VEGF in a prospective series of age-related macular degeneration (AMD) patients and found that the VEGF levels were much lower in bevacizumab than ranibizumab patients.[5] Zehetner *et al* found reduced plasma VEGF following injections of bevacizumab, but not ranibizumab or pegaptanib at 1 week and 1 month after treatment of diabetic macular oedema.[6] IVAN, the largest study to date to measure serum VEGF levels in AMD, reported a reduction of 69% for bevacizumab and 20% for ranibizumab at 1 year, and a reduction of 78% for bevacizumab and 28% for ranibizumab at 2 years.[7 8] In a small prospective study, we recently reported reduced plasma VEGF levels following bevacizumab and aflibercept injections, but with minimal reduction following ranibizumab injections (Avery *et al*[9]). The effect was most prominent for aflibercept, where a dramatic reduction was noted 3 h after the first injection and persisted at 1, 3 and 7 days. The effect of bevacizumab was less dramatic after the first dose, but after the third monthly dose, systemic accumulation of bevacizumab was noted, and the reduction in VEGF was similar to that of aflibercept. In this study, the concentration of bevacizumab after the third dose exceeded the half maximal inhibitory concentration (IC_{50}) for VEGF, and coincided with the more dramatic reduction in plasma VEGF levels. The concentration of aflibercept after both the first and third doses exceeded the IC_{50}, and corresponded to a marked reduction in plasma VEGF levels.

Many authors have measured systemic VEGF levels given the commercial availability of antibodies to VEGF; however, correlation to anti-VEGF drug levels is less commonly reported because it is more difficult to obtain antibodies to these agents. Nevertheless, the measurement of VEGF levels in the bloodstream is complex, and although different authors have reported similar relative results, the absolute VEGF concentration varies dramatically between studies. One obvious reason for this difference is the platelet—which contains large concentrations of VEGF. IVAN, which measured serum VEGF, reported very high VEGF levels, in part because the measurement included VEGF released from platelets.[7] Even plasma levels of VEGF vary between studies, in part because different anticoagulants are better than others for preventing platelet activation.[10] Despite the variation in absolute VEGF levels between studies, the recurrent finding is that bevacizumab lowers systemic VEGF levels much more than ranibizumab.[5 6 7 8 9] The most probable reason for this finding relates to the systemic half-life of the drugs. Bevacizumab and aflibercept contain an Fc fragment that binds an endothelial cell receptor and is recycled—thereby prolonging systemic half-life. Ranibizumab, on the other hand, lacks the Fc fragment and has a markedly shorter intrinsic systemic half-life.[11] In our recent human study, we measured the systemic exposure (AUC) after the third monthly intravitreal injection to be 13-fold greater for aflibercept than ranibizumab and 70-fold greater for bevacizumab than ranibizumab (Avery *et al*[9]). These findings along with aflibercept's higher binding affinity help explain the observed differences in plasma VEGF levels.

Other studies have demonstrated differences between the drugs. Campochiaro and colleagues

Open Access
Scan to access more free content

CrossMark

To cite: Avery RL. *Br J Ophthalmol* 2014;**98**:i7–i10.

showed a strong fellow eye effect following intravitreal injection of bevacizumab, but not ranibizumab, in two transgenic mice models secreting human VEGF.[12] Interestingly, in the more severe model, the eyes receiving saline injection whose fellow eye had received a bevacizumab injection had a better outcome than those eyes that received a direct ranibizumab injection. In other words, the fellow eye effect of bevacizumab was stronger than direct injection of ranibizumab. In rabbits and monkeys, bevacizumab has been detected in fellow eyes after intravitreal injection, but not ranibizumab[13] (Avery *et al*[14]). In the CATT trial, fellow eyes were evaluated to determine if there was a difference in the development of choroidal neovascularisation (CNV).[15] Although the difference was not statistically significant, at 2 years, the incidence of fellow eye CNV was diverging—developing in 20.6% of ranibizumab patients, and in 16.6% of bevacizumab patients, consistent with a potential protective effect of systemic bevacizumab. In addition, intravitreal bevacizumab, but not ranibizumab, was recently reported to reduce fellow eye thickness in a study of diabetic macular oedema (DME) patients.[3]

One reason many clinicians discount fellow eye effects could be due to the Food and Drug Administration (FDA) labels for Lucentis and Eylea which imply that these drugs do not reach concentrations high enough to have a systemic effect. The Lucentis label states, 'In patients with neovascular AMD, following monthly intravitreal administration, maximum ranibizumab serum concentrations were low (0.3 ng/mL to 2.36 ng/mL). These levels were below the concentration of ranibizumab (11 ng/mL to 27 ng/mL) thought to be necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay' (IC_{50}).[16] However, a recent publication from Genentech cited the IC_{50} to be 3 ng/mL,[17] and in new assays, they have reported the IC_{50} of ranibizumab to be as low as 1.5 ng/mL.[18] Recently, pharmacokinetic data from the HARBOR study have been presented which show a number of individual patients receiving 0.5 or 2.0 mg ranibizumab were found to have serum ranibizumab levels a month after the last injection that exceed these IC_{50} levels for VEGF of 1.5 or even 3 ng/mL (Avery[19]). These findings raise the possibility of a systemic effect despite the current Lucentis label.

The Eylea label states, 'It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half maximally bind systemic VEGF.'[20] However, the label states that the mean maximum plasma concentration of free aflibercept after injection for AMD or retinal vein occlusion (RVO) was 20–50 ng/mL, which is over 10-fold higher than ranibizumab, and more importantly, more than 10-fold over the reported IC_{50} of aflibercept for VEGF (1.8 ng/mL).[21] Given this relationship and the multiple studies showing a reduction in systemic VEGF after intravitreal bevacizumab, it is not surprising to observe a similar effect with aflibercept. In trying to reconcile the observation of dramatically reduced plasma VEGF levels after intravitreal aflibercept and the claim that the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half maximally bind systemic VEGF, it seems that the claim is based on a complex pharmacokinetic model of data following administration of large systemic doses of aflibercept.[22] However, despite the label and the model upon which it is based, the finding of markedly reduced VEGF levels makes the possibility of a fellow eye effect or other systemic effect biologically plausible.

A critical question arises, if VEGF levels are indeed reduced after intravitreal injection, 'So what?' We know that systemic administration of these agents is beneficial to cancer patients, and even with doses hundreds or even a thousand fold higher than intravitreal doses, the side effects are tolerable. Nevertheless, there are black box warnings such as severe bleeding, including central nervous system haemorrhage, and death with systemic administration.[23 24] Fortunately, in all intravitreal anti-VEGF registration trials, the incidence of the most important side effects, including cerebrovascular accident (CVA), myocardial infarction and death, has not been found to be significantly elevated (although the studies lack the power to adequately assess small differences in these uncommon events).[25] Of course, bevacizumab did not undergo registration trials for intravitreal use, but we can evaluate its safety based upon the comparative trials, CATT, IVAN, MANTA and GEFAL.[26] Most importantly, there was no safety signal for bevacizumab for any of the arteriothrombotic events (ATEs) or expected complications of systemic VEGF suppression. However, at 1 year, CATT reported that the bevacizumab treated patients had an increased incidence of systemic serious adverse events (SAEs) which were noted across many organ systems (and not necessarily related to known anti-VEGF complications).[27] This difference was hard to interpret, but persisted and somewhat increased at year 2.[28] A similar difference was also observed in IVAN at year 1.[7] When taken into account with the CATT data, the IVAN data safety monitoring committee informed patients that this difference was not felt to be due to chance.[29] Fortunately, by year 2 of IVAN, the imbalance had dissipated.[30] When looking at a meta-analysis of the four comparative trails at 1 year, the imbalance was consistent across all four, and was found to be statistically significant with an OR of 1.34.[26] Similarly, the meta-analysis of the 2-year trials, CATT and IVAN, also showed a statistically significant increase in risk of systemic SAEs with bevacizumab versus ranibizumab.[30] The CATT trial noted more systemic SAEs in the as-needed arm than the monthly arm, and commented that this lack of a dose response made causality less likely.[27] However, the IVAN trial also found the arm had a significantly higher risk of death and ATEs than the monthly arm, and despite other advantages of dosing, the final recommendation is for monthly dosing due to this increased risk of death.[30] Again, these findings may be hard to interpret, but VEGF's role in systemic disease may be more complex than in the eye, and it is conceivable that fluctuations in VEGF levels are of more concern than chronic suppression. Nevertheless, the IVAN study's recommendation to alter dosing based upon ATEs or death rates clearly implies that there must be a belief that there is a systemic effect of these intravitreal agents.

If indeed there are systemic effects of these agents, where might we expect them to be relevant? One patient population of concern is retinopathy of prematurity (ROP) where intravitreal bevacizumab use is increasing. Several years ago, I suggested using lower doses of anti-VEGF agents in ROP based upon my observations of the effects of lower doses on retinal neovascularisation in PDR.[31] The BEAT-ROP trial demonstrated bevacizumab's efficacy in treating posterior ROP, but discounted potential safety concerns, stating that due to bevacizumab's large size, it 'cannot penetrate the intact retina or escape the eye except in very small amounts.'[32] I do not believe this to be correct as we had previously demonstrated penetration through the retina, and others had demonstrated that the Fc receptor could facilitate transport of antibodies from the vitreous across the retinal vasculature's endothelium into the circulation.[33 34] Furthermore, studies have now measured bevacizumab in the bloodstream after intravitreal injection for ROP with a

significant reduction in VEGF levels.[35] In addition, fellow eye effects have also been reported in ROP.[36] These immature babies are still undergoing organogenesis, and VEGF is involved in many processes, including lung maturation.[11] In BEAT-ROP, there was an imbalance in deaths, with two in the laser arm and five in the bevacizumab arm, and this imbalance was more notable in respiratory deaths (one in the laser arm and four in the bevacizumab arm); however, these differences did not reach statistical significance.[32] An additional reason to reconsider dosing was provided by Lutty *et al* who used a canine model of ROP that mimics the size of human ROP eyes.[37] He showed that 5 μg of intravitreal VEGF trap inhibits the abnormal retinal neovascularisation without impairing retinal vasculogenesis or revascularisation as did higher doses. Hence, it seems reasonable to consider lower doses of anti-VEGF agents in treating ROP if not also using an agent with less systemic exposure.[38]

Another group of patients of concern are those at risk for stroke. An interim analysis of the SAILOR trial produced a 'dear doctor' warning letter about the potential increased risk of CVA with 0.5 mg of ranibizumab versus 0.3 mg. However, by the end of the trial, the numbers were no longer statistically significant.[39] A meta-analysis of SAILOR and four other AMD trials found no statistically increased risk of stroke with the higher dose of ranibizumab unless the patients were stratified with respect to their baseline stroke risk.[40] Within the group of patients at the highest risk of stroke, those patients treated with 0.5 mg of ranibizumab had a higher stroke rate versus sham treatment with an OR of 7.7.[40] Many subsequent trials have excluded patients with recent strokes, as this population may have up to a 10-fold increased risk of stroke.[41] Age is another risk factor for stroke.[41] When the VIEW studies were evaluated by the European Public Assessment Report and broken down by age, an imbalance was seen in the rate of cerebral vascular events in those over 85 years of age receiving aflibercept and ranibizumab.[42] At 1 year, this rate was 1.2% for ranibizumab and 7.1% for aflibercept, and at 2 years this rate was 3.4% for ranibizumab and 9.5% for aflibercept. This evaluation included transient ischaemic attacks (TIAs) that are not included in Antiplatelet Trialists' Collaboration (APTC) events, and as many of these patients suffered TIAs, this imbalance was not noted in APTC event rates. Diabetic patients have an inherent increased risk of stroke, and when they were studied in the RISE/RIDE trials of ranibizumab, an imbalance between stroke and death rates between 0.5 and 0.3 mg arms was noted and prompted Genentech to seek FDA approval of the 0.3 mg dose for DME.[43] A meta-analysis of 14 trials of ranibizumab where pairwise comparisons are available has recently been presented. This study of over 6500 patients showed no significant imbalances in the AMD and RVO patients, but in those with DME, imbalances were noted with respect to wound healing, stroke and death.[44] Sixteen patients in the 0.5 mg ranibizumab arm developed wound-healing complications, while only two did in the 0.3 mg arm, and none did in the sham arm.[44]

Still larger numbers of patients have been evaluated in meta-analyses of Medicare databases to look for any differential risk of stroke between bevacizumab and ranibizumab use.[45] Unfortunately, it is very difficult to completely correct for biases such as socioeconomic status, which could affect the choice of drug and also impact the baseline risk of stroke. Hence, these studies are of limited value. With the widespread use of electronic medical records, hopefully registries will be used in the future to allow analysis of large numbers with more precise patient specific data. Analysis of large populations will be critical to identify if there is a systemic risk to these intravitreal agents, as individual trials are not powered to detect differences in uncommon events.

In summary, anti-VEGF therapy has revolutionised the treatment of retinal disease, and its impact is probably even greater in the retinal world than in oncology where these agents were first developed. The small doses used for eye disease seem to be safe, but these agents are very potent. Numerous studies show reduced systemic VEGF levels after intravitreal injections, and the systemic effect of ranibizumab appears to be the lowest, consistent with pharmacological differences between the agents. The trials comparing ranibizumab to bevacizumab have found an imbalance in development of systemic SAEs, which is biologically plausible based upon the differences in systemic VEGF levels. However, the significance of these SAEs remains unclear. There may be subsets of patients, such as ROP babies, patients with diabetes, the elderly or those with recent ATEs such as stroke, who may be at increased risk after intravitreal anti-VEGF injection, but further studies are required to evaluate this potential risk.

Correction notice This article has been corrected since it was published Online First. The sentence 'The CATT trial noted more systemic SAEs in the arm than the monthly arm' has been corrected to 'The CATT trial noted more systemic SAEs in the as-needed arm than the monthly arm'.

Competing interests RLA reports personal fees from Alcon, grants and personal fees from Allergan, grants, personal fees and non-financial support from Genentech, personal fees and non-financial support from Novartis, personal fees from Ophthotech, grants, personal fees and non-financial support from Regeneron, personal fees and non-financial support from Replenish, outside the submitted work; in addition, RLA has patents on intravitreal drug delivery licensed to Replenish.

Funding None.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1 Avery RL, Pearlman J, Pieramici DJ, *et al*. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology* 2006;113:1695–705.
2 Acharya NR, Sittivarakul W, Qian Y, *et al*. Bilateral effect of unilateral ranibizumab in patients with uveitis-related macular edema. *Retina* 2011;31:1871–6.
3 Bakbak B, Ozturk BT, Gonul S, *et al*. Comparison of the effect of unilateral intravitreal bevacizumab and ranibizumab injection on diabetic macular edema of the fellow eye. *J Ocul Pharmacol Ther* 2013;29:728–32.
4 Matsuyama K, Ogata N, Matsuoka M, *et al*. Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab. *Br J Ophthalmol* 2010;94:1215–18.
5 Carneiro AM, Costa R, Falcão MS, *et al*. Vascular endothelial growth factor plasma levels before and after treatment of neovascular age-related macular degeneration with bevacizumab or ranibizumab. *Acta Ophthalmol* 2012;90:e25–30.
6 Zehetner C, Kirchmair R, Huber S. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema. *Br J Ophthalmol* 2013;97:454–9.
7 Chakravarthy U, Harding SP, Rogers CA, *et al*. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;119:1399–411.
8 Harding SP. IVAN Outcomes [abstract]. *Invest Ophthalmol Vis Sci* 2013;54. ARVO E-Abstract.
9 Avery RL, Castellarin A, Steinle N, *et al*. Comparison of Systemic Pharmacokinetics Post Anti-VEGF Intravitreal Injections of Ranibizumab, Bevacizumab and Aflibercept (abstract). *Presented at the 2013 Annual Meeting of the American Society of Retina Specialists (ASRS)*; Toronto, 25 August 2013.
10 Zimmermann R, Koenig J, Zingsem J, *et al*. Effect of specimen anticoagulation on the measurement of circulating platelet-derived growth factors. *Clin Chem* 2005;51:2365–8.
11 Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol* 2011;56:95–113.
12 Miki K, Miki A, Matsuoka M, *et al*. Effects of intraocular ranibizumab and bevacizumab in transgenic mice expressing human vascular endothelial growth factor. *Ophthalmology* 2009;116:1748–54.

13 Bakri SJ, Snyder MR, Reid JM, *et al*. Pharmacokinetics of intravitreal ranibizumab (Lucentis). *Ophthalmology* 2007;114:2179–82.
14 Avery RL, Le K, Lu T, *et al*. Visual Acuity Response as a Function of the Affinity and Vitreous Half-Life of Intravitreally-Administered Anti-VEGF Agents (abstract). *Presented at the ASRS*; Las Vegas, 28 August 2012.
15 Maguire MG, Daniel E, Shah AR, *et al*. Incidence of choroidal neovascularization in the fellow eye in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2013;120:2035–41.
16 Lucentis US Prescribing Information 2013, page 10. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125156s081lbl.pdf (accessed 9/10/2013).
17 Yu L, Liang XH, Ferrara N. Comparing protein VEGF inhibitors: In vitro biological studies. *Biochem Biophys Res Commun* 2011;408:276–81.
18 Tuomi L, Zhang Y, Visich J. Pharmacokinetics of intravitreal ranibizumab in patients with neovascular age-related macular degeneration, retinal vein occlusion, and diabetic macular edema [abstract]. *Invest Ophthalmol Vis Sci* 2012;53 ARVO E-Abstract 4178.
19 Avery RL. Anti-Therapeutic Antibody Analyses of Ranibizumab 0.5 mg or 2.0 mg in Patients With Wet Age-related Macular Degeneration. *Presented at Angiogenesis, Exudation, and Degeneration 2013*, Miami Fla, 9 Feb 2013.
20 Eylea US Prescribing Information 2013, page 15. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125387s015s020lbl.pdf (accessed 9/10/2013).
21 Papadopoulos N, Martin J, Ruan Q, *et al*. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 2012;15:171–85.
22 Thai H-T, Veyrat-Follet C, Vivier N, *et al*. A mechanism-based model for the population pharmacokinetics of free and bound aflibercept in healthy subjects. *Br J Clin Pharmacol* 2011;72:402–14.
23 Avastin US Prescribing Information 2013, page 3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125085s267lbl.pdf (accessed 9/10/2013).
24 Zaltrap US Prescribing Information 2013, page 1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125418s000lbl.pdf (accessed 9/10/2013).
25 Schmucker C, Ehlken C, Agostini HT, *et al*. A safety review and meta-analyses of bevacizumab and ranibizumab: off-label versus goldstandard. *PLoS ONE* 2012;7:e42701.
26 Kodijian L. GEFAL Outcomes. *IOVS* 2013;54. ARVO E-Abstract.
27 Martin DF, Maguire MG, Ying GS, *et al*. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;364:1897–908.
28 Martin DF, Maguire MG, Fine SL, *et al*. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388–98.
29 http://cteu.bris.ac.uk/trials/ivan/PIGPSafetyLetter.pdf (accessed 9/10/2013).
30 Chakravarthy U, Harding SP, Rogers CA, *et al*. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet* 2013;382:1258–67.
31 Avery RL. Extrapolating anti-vascular endothelial growth factor therapy into pediatric ophthalmology: promise and concern. *J AAPOS* 2009;13:329–31.
32 Mintz-Hittner HA, Kennedy KA, Chuang AZ, *et al*. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011;364:603–15.
33 Shahar J, Avery RL, Heilweil G, *et al*. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin®). *Retina* 2006;26:262–9.
34 Kim H, Robinson SB, Csaky KG. FcRn receptor-mediated pharmacokinetics of therapeutic IgG in the eye. *Mol Vis* 2009;15:2803–12.
35 Sato T, Wada K, Arahori H, *et al*. Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. *Am J Ophthalmol* 2012;153:327–33.
36 Karaca C, Oner AO, Mirza E, *et al*. Bilateral effect of unilateral bevacizumab injection in retinopathy of prematurity. *JAMA Ophthalmol* 2013;131:1099–101.
37 Lutty GA, McLeod DS, Bhutto I, *et al*. Effect of VEGF trap on normal retinal vascular development and oxygen-induced retinopathy in the dog. *Invest Ophthalmol Vis Sci* 2011;52:4039–47.
38 Avery RL. Bevacizumab (Avastin) for retinopathy of prematurity: wrong dose, wrong drug, or both? *J AAPOS* 2012;16:2–4.
39 Boyer DS, Heier JS, Brown DM, *et al*. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. *Ophthalmology* 2009;116:1731–9.
40 Bressler NM, Boyer DS, Williams DF, *et al*. Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. *Retina* 2012;32:1821–8.
41 Alexander SL, Linde-Zwirble WT, Werther W, *et al*. Annual rates of arterial thromboembolic events in medicare neovascular age-related macular degeneration patients. *Ophthalmology* 2007;114:2174–8.
42 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002392/WC500135744.pdf (accessed 9/10/2013).
43 Brown DM, Nguyen QD, Marcus DM, *et al*. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013;120:2013–22.
44 Avery R, Francom S, Tuomi L, *et al*. Meta-analysis examining the systemic safety profile of intravitreal ranibizumab injections in AMD, RVO, and DME [abstract]. *IOVS* 2013;54:ARVO E-Abstract 1535.
45 Curtis LH, Hammill BG, Schulman KA, *et al*. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol* 2010;128:1273–9.