Table 1. Risk of ischaemic stroke associated with the intravitreal use of bevacizumab.

Ischaemic Stroke (N = 1856)						
Bevacizumab (Avastin)	Used only in the case period	Used only in the control period	Used in both periods	Not used in either period	Adjusted OR	95% CI
4-week window period*	4	3	0	20	1.33	0.29, 5.95 (Mid-p Exact)
8-week window period†	5	3	0	19	1.66	0.39, 6.97 (Mid-p Exact)

PS: Conditional logistic regression was used to adjust for important potential confounding variables including diabetes mellitus, hypertension, lipid metabolism disorder, chronic renal disease, antihypertensive drugs, antidiabetic drugs and lipid lowering drugs between the case and control periods.

*Case period was defined as 1–30 days before the index date, and the control period was defined as 121–150 days before the index date.

†Case period was defined as 1–60 days before the index date, and the control period was defined as 91–150 days before the index date.

other medication from the database. The definition of the case period is based on the pharmacokinetics of bevacizumab. The maximum serum concentration has been found to be achieved 8 days after intravitreal injection, and the elimination of bevacizumab in serum parallels the level found in the vitreous humour and has been found to fall below 1 mg/ml at 29 days after injection (Bakri et al. 2007). We compared bevacizumab use between the case and control periods and calculated the OR and 95% CI by conditional logistic regression. Statistical analyses were performed using SPSS version 16.0.1 (SPSS Inc, Chicago, IL, USA, 2007).

We identified 1,856 patients who matched our criteria (62% male, mean age 71.2 years [SD = 13.9]). Among these cases, intravitreal bevacizumab was prescribed to 27 (1.4%) of the patients. In Table 1, it can be seen that there is no significant increase in the risk of ischaemic stroke associated with the use of intravitreal bevacizumab. The incidence of ischaemic stroke after intravitreal injection of bevacizumab is very low but seems to mostly occur during the first month after injection. Campbell et al. (2012) documented a time series analysis that showed that neither the trend nor the level of the stroke in the time series changed with the uptake of bevacizumab. Compared with ranibizumab, which is another anti-VEGF agent specifically designed to treat AMD, bevacizumab has been reported in the CATT as having a higher proportion of patients with serious systemic adverse events (CATT Research Group et al. 2011). Rate of myocardial infarction, which shares a similar thromboembolic mechanism to that of ischaemic stroke, was higher for an anti-VEGF group than a photodynamic therapy group and a community group in the study by Kemp and colleagues (Kemp et al. 2013); however, the author was not able to show that the results were related to anti-VEGF management and not the underlying diseases themselves.

There were several limitations to this study. First, we did not have information on some risk factors, including blood pressure, glycemic control, body mass index, smoking and alcohol consumption. However, such personal lifestyle factors are unlikely to change substantially during short-term observation, and this would also be partially controlled by the case-crossover design. Second, we could not exclude unmeasured or residual confounders that have not been discussed in the study.

In conclusion, intravitreal bevacizumab use for the treatment of AMD and diabetic macular oedema is not associated with a change in the rate of ischaemic stroke among patients attending Taipei City Hospital. Further randomized controlled trials are required to evaluate and validate these results.

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Antisepsis with polyhexanide is effective against endophthalmitis after intravitreal injections

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doi: 10.1111/aos.12347

Dear Editor,

After intravitreal injections (IVIs) with antivascular endothelial growth factor (anti-VEGF) agents, the most feared complication is infectious endophthalmitis. For endophthalmitis prophylaxis, povidone–iodine has been widely used. While allergic reactions after the use of povidone–iodine are rare, it is a regular clinical observation that the irritant effect to the ocular surface is a common complaint of patients (Wykoff et al. 2011). As pain is a common symptom of endophthalmitis, surface irritation after

povidone–iodine is often confused with endophthalmitis-initiated pain.

Due to its local tolerance and its effectiveness, polihexanide (Lavasept, B. Braun AG, Melsungen, Germany) may be an alternative agent. In a randomized clinical trial, polihexanide was effective against microbes with a significantly higher reduction in pathogens than povidone–iodine and a longer duration of antisepsis (Hansmann et al. 2005).

In this retrospective follow-up chart review, we evaluate the effectiveness of antisepsis with polihexanide to prevent endophthalmitis after IVIs with anti-VEGF agents.

All consecutive IVIs that were performed in the University Hospital Cologne between January 2007 and September 2013 with preoperative antisepsis with polyhexanide and the anti-VEGF drugs bevacizumab, ranibizumab and aflibercept were included. The study adhered to the tenets of the Declaration of Helsinki.

Before IVIs were administered in an operating room, polyhexanide 0.04% was applied three times in intervals of ten minutes. Physicians and nurses wore caps and surgical masks. IVI was performed using a lid speculum and a 30-gauge needle after conjunctival anaesthesia. Contact between needle and eyelid or lashes was strictly avoided. Ofloxacine eye drops were used for three days after IVI until March 2013 because of evidence of drug-resistant bacteria after repeated application of antibiotic eye drops. After injection, patients were informed about the symptoms of endophthalmitis and instructed to consult our clinic immediately if symptoms appeared.

Statistical analysis was performed using SPSS software, version 21.0 (IBM Software and Systems, Armonk, NY, USA). Confidence intervals (CIs) were calculated using the Wilson score method without continuity correction. Endophthalmitis rates were compared with the chi-square test.

A total of 13 436 IVIs with an anti-VEGF agent and antisepsis with polyhexanide were performed. Bevacizumab was injected in 1538 (11.4%) cases, ranibizumab in 11 272 (83.9%) cases and aflibercept in 626 (4.7%) cases.

Five cases of post-IVI endophthalmitis occurred which resulted in a rate of 0.037% (95% CI 0.016–0.088%) or 1 case per 2687 IVIs. Endophthalmitis rates after IVIs using antisepsis with povidone–iodine in studies with >5000 injections are summarized in Table 1. There was no significant difference between the two antisepsis groups ($p = 0.86$).

Table 1. Endophthalmitis rates in clinical trials with >5000 IVIs.*

Study	Number of IVIs	Endophthalmitis cases	Endophthalmitis rate (%)	Antisepsis
Rosenfeld et al. (MARINA)	10 443	5	0.048	Povidone-iodine
Fintak et al.	26 905	6	0.022	
Pilli et al.	10 254	3	0.029	
Klein et al.	30 736	15	0.049	
Moshfegi et al.	60 322	12	0.020	
Shah et al.	27 736	23	0.083	
Chen et al.	29 995	11	0.037	
Martin et al. (CATT)	17 217	11	0.064	
Cheung et al.	14 893	7	0.047	
Heier et al. (VIEW 1 + 2)	26 832	6	0.022	
Casparis et al.	40 011	3	0.007	
Shimada et al.	15 144	0	0.000	
Mason et al.	5233	1	0.022	
Brown et al. (ANCHOR)	5921	3	0.096	
Inoue et al.	5236	5	0.095	
Bhatt et al.	7054	5	0.071	
Lad et al.	8802	8	0.045	
Total	342 734	124	0.036	
University Hospital of Cologne	13 436	5	0.037	Polihexanide

IVI, intravitreal injection.
*Modified from Shimada et al. (2013) and Casparis et al. (2014).

In four of five cases, the causing pathogen could be detected by vitreous cultures. All cases with endophthalmitis occurred after injections of ranibizumab. Comparison between ranibizumab (5 in 11 272) and non-ranibizumab (0 in 2164) did not show a statistically significant difference ($p = 0.42$).

In our study, we demonstrated a low rate of endophthalmitis after IVIs with anti-VEGF agents using polihexanide for antisepsis, which was comparable with the incidence in previous studies using povidone–iodine. We have made the observation that polihexanide is less irritant to the ocular surface resulting in less discomfort and pain. As pain is a major symptom of endophthalmitis, this results in less false-positive cases of suspected endophthalmitis and subsequent unnecessary and possibly harming treatment. Less discomfort may also increase adherence to therapy. However, in the preoperative preparation, polihexanide needs a longer residence time than povidone–iodine. In a comparative study, threefold application was performed showing conjunctival antisepsis after ten-minute latency (Hansmann et al. 2005). In summary, antisepsis with polihexanide is as effective as povidone–iodine in preventing endophthalmitis. As it is less irritant to the ocular surface, it could be used as a standard agent for antisepsis in ophthalmology.

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Bevacizumab versus diode laser in stage 3 posterior retinopathy of prematurity

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doi: 10.1111/aos.12339

Editor,

Anti-VEGF agents, primarily bevacizumab, are emerging as a successful therapy for retinopathy of prematurity (ROP), particularly in aggressive posterior disease (Spandau et al. 2013). Concerns exist however regarding dosage, timing, duration of follow-up and long-term visual function.

We conducted a prospective case–control study in 14 infants with symmetrical zone 1 or posterior zone 2 Stage 3 + ROP; comparing intravitreal bevacizumab in one eye to laser therapy in the fellow eye. The purpose was to evaluate anatomic outcomes (regression or recurrence of ROP), and functional visual outcomes in the bevacizumab-treated eyes compared with laser-treated eyes, at one- and 2-year follow-up. We also evaluated ocular, systemic and developmental outcomes at one- and 2-year follow-up. Four infants had symmetrical Zone 1 Stage 3 + disease and 10 infants had Zone 2 Stage 3 + disease (Fig. 1).

We randomized the eyes into intravitreal bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA) versus conventional laser therapy. All procedures were performed in the special-care baby unit (SCBU) under morphine sedation. Intravitreal injection with bevacizumab was performed under aseptic technique using a dose of 1.25 mg in 0.1 ml. After injection of bevacizumab, conventional 360° laser treatment was applied to the fellow eye.

The eyes were monitored weekly for 8 weeks, 3 monthly for a further 12 months, and 3–6 monthly thereafter. At 1- and 2-year follow-up, a full ocular examination was performed. Electrophysiology testing, visual evoked potential (VEP) and electroretinography (ERG), was performed on each eye where possible. All of the babies had a paediatric examination and magnetic resonance (MR) brain scan.

We observed rapid regression of ROP in all eyes injected with bevacizumab, as well as resolution of plus disease and flattening of the ridge by 48 hr postinjection in all eyes. Further vascularization was noted with complete regression taking up to sixty weeks in some eyes.

In our study, four of 14 eyes (28.6%) had recurrence of ROP; three eyes (21.42%) which had bevacizumab treatment and one eye (7.14%) with conventional laser therapy. There was a significant time delay to recurrence in the bevacizumab group compared with laser, with a mean age of 51 weeks PMA at time of recurrence in bevacizumab-treated eyes compared with 37 weeks PMA in the laser-treated eye. This delay in recurrence has also been reported by other studies including the BEAT-ROP trial. (Mintz-Hittner et al. 2011). Of the 3 bevacizumab-treated eyes with recurrence, two eyes received laser treatment where the ROP was peripheral. One eye with more posterior recurrence received a further intravitreal bevacizumab injection. In the eyes that received laser treatment, one eye (7.14%) demonstrated recurrent

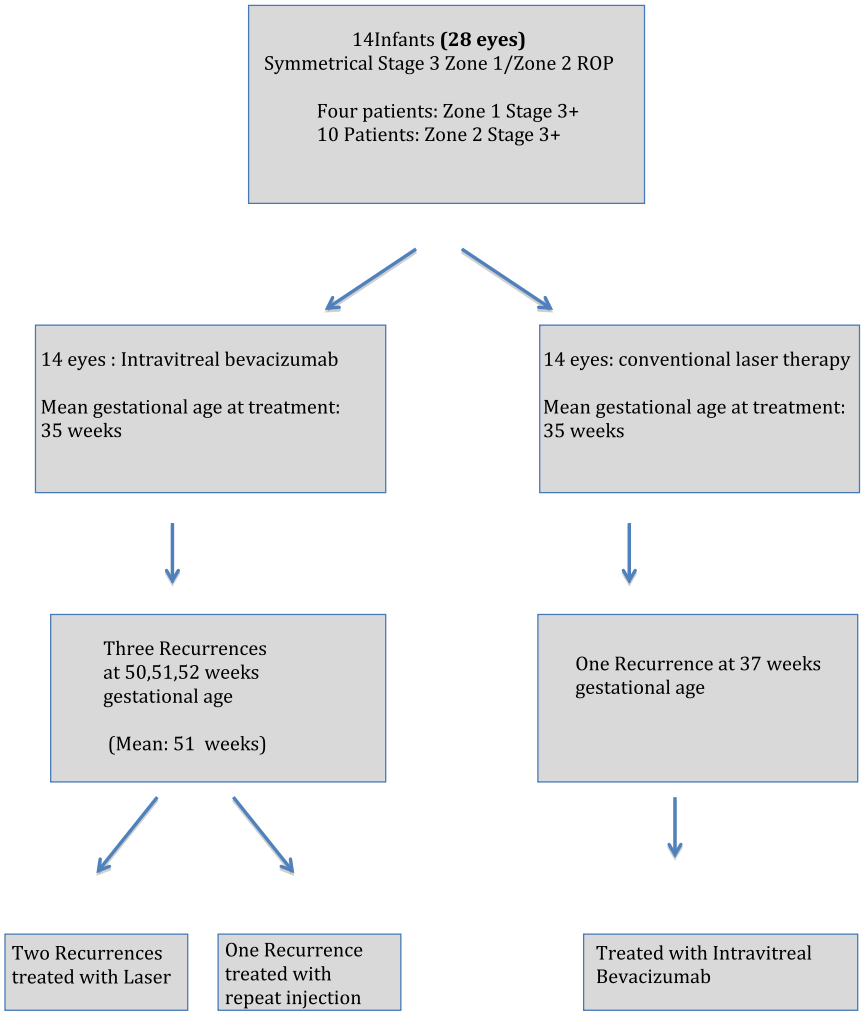

Fig. 1. Summary of eyes treated, including recurrences, bevacizumab and laser.