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Systemic Vascular Safety of Ranibizumab for Age-Related Macular Degeneration

Systematic Review and Meta-analysis of Randomized Trials

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Background: We conducted a meta-analysis of randomized trials of ranibizumab for age-related macular degeneration (AMD) to elucidate systemic vascular risk.

Clinical Relevance: Although intravitreal vascular endothelial growth factor inhibitors are widely used to treat AMD, whether they produce systemic adverse effects remains uncertain.

Methods: We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials through March 2014 to identify the randomized trials that compared systemic safety among different intensities of ranibizumab treatment for AMD. The outcome measures were the incidence of cerebrovascular accidents (CVAs), myocardial infarctions, nonocular hemorrhages, overall arterial thromboembolic events (ATEs), and all-cause mortality. We calculated the Peto odds ratio (OR) with 95% confidence interval for the comparisons between different intensities of regimens in terms of dose and retreatment frequency.

Results: Eleven trials comprising 6596 patients with AMD were included in the meta-analysis. A significant increase was observed in the following comparisons: 0.5 versus 0.3/0.0 mg for CVA (OR, 1.86; 95% CI, 1.05−3.29; $P = 0.03$), monthly versus pro re nata (PRN)/0.0 mg for CVA (OR, 1.89; 95% CI, 1.06−3.38; $P = 0.03$), and 0.3/0.5 versus 0.0 mg for nonocular hemorrhage (OR, 1.57; 95% CI, 1.01−2.44; $P = 0.04$). A nonsignificant increase was observed in the following comparisons: 0.5 versus 0.0 mg for CVA (OR, 2.27; 95% CI, 0.90−5.69; $P = 0.08$), monthly versus PRN for CVA (OR, 2.04; 95% CI, 0.94−4.45; $P = 0.07$), 0.5 versus 0.0 mg for nonocular hemorrhage (OR, 1.68; 95% CI, 0.98−2.88; $P = 0.06$), 0.3 versus 0.0 mg for nonocular hemorrhage (OR, 1.68; 95% CI, 0.95−2.98; $P = 0.07$), monthly versus PRN/0.0 mg for nonocular hemorrhage (OR, 1.54; 95% CI, 0.98−2.42; $P = 0.06$), monthly versus PRN for ATE (OR, 1.58; 95% CI, 0.96−2.61; $P = 0.07$), and monthly versus PRN/0.0 mg for ATE (OR, 1.42; 95% CI, 0.99−2.05; $P = 0.06$). Among the other analyses, no protective or harmful effects of ranibizumab were observed.

Conclusions: In ranibizumab treatment for patients with AMD, a possible relationship of more intensive treatment to more systemic vascular adverse events was identified, but no relationship with mortality was identified. *Ophthalmology 2014;121:2193-2203 © 2014 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Age-related macular degeneration (AMD) is a leading cause of blindness worldwide.[1] After establishment of its efficacy to treat exudative AMD,[2,3] ranibizumab has been the most widely used[4] intravitreal vascular endothelial growth factor (VEGF) inhibitor that has received approval from the US Food and Drug Administration (FDA). Ranibizumab has also been the most intensively evaluated drug for its efficacy and safety through numerous randomized trials.

Despite the unquestionable effectiveness of VEGF inhibitors in restoring and improving the vision of patients with exudative AMD, as long as treatment frequency is maintained, the possible adverse effects on the systemic vasculature remain uncertain.[5−12] Some reports[6,7] have indicated an increased risk of cerebrovascular events with ranibizumab, whereas other postmarketing retrospective studies[9−11] have reported conflicting results.

The results of our previous meta-analysis of 3 randomized controlled trials indicated a significant increase in cerebrovascular accidents (CVAs) in response to ranibizumab treatment.[6] In contrast, in other meta-analysis reports, cerebrovascular and cardiovascular risks were not specifically evaluated.[13,14] In addition, non-AMD patients were included and different pharmacologic types of VEGF inhibitors were collectively discussed.[15] Since then, several other randomized trials investigating ranibizumab for AMD have been published; thus, we performed an updated meta-analysis to address the systemic risks associated with ranibizumab administration for patients with AMD.

Methods

We conducted a systematic review and meta-analysis based on a predefined protocol (Appendix 1; available at www.aaojournal.org).

http://dx.doi.org/10.1016/j.ophtha.2014.05.022
ISSN 0161-6420/14

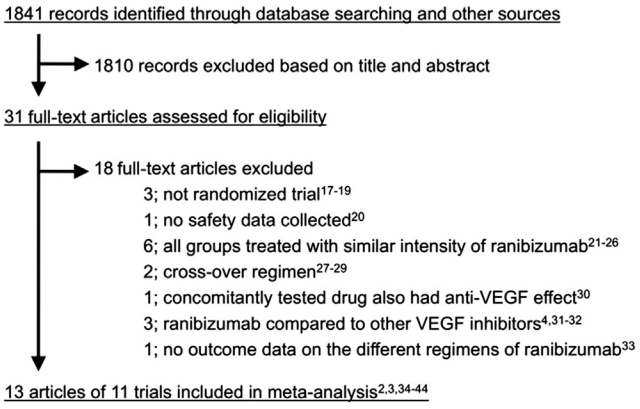

Figure 1. Selection of studies. VEGF = vascular endothelial growth factor.

Literature Search

We systematically searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases with no language restrictions from inception until March 2014. The key terms used for the systematic search were "macular degeneration," "choroidal neovascularization," and "ranibizumab," while restricting the search to randomized trials. The detailed search strategy is described in the protocol presented in Appendix 1 (available at: www.aaojournal.org). Two independent reviewers (T.U. and T.T.) performed the electronic searches. First, we assessed titles and abstracts and excluded reports that were apparently not randomized trials on ranibizumab use for AMD. After the initial screening, we retrieved full reports and assessed for eligibility. We also searched the reference lists of original studies and review articles identified by the electronic search for other potentially eligible articles.

Table 1. Characteristics of Included Studies

No. of Patients by Study	Dose/Injection	No. of Injections	Follow-up (mo)	Mean Age (yr)	Completion Rate (%)	Support by Manufacturers
MARINA 2006[2]						Yes
236	Sham	0	24	77	79.8	
238	0.3 mg	24	24	77	88.2	
239	0.5 mg	24	24	77	89.6	
FOCUS 2008[36,37]						Yes
56	PDT	0	24	73	85.2	
105	0.5 mg + PDT	24	24	75	85.2	
PIER 2008[38]						Yes
63	Sham	0	12	78	86	
59	0.3 mg	6	12	79	97	
61	0.5 mg	6	12	79	97	
ANCHOR 2006, 2009[3,35]						Yes
143	PDT	0	24	78	76.9	
137	0.3 mg	24	24	77	83.6	
140	0.5 mg	24	24	76	82.9	
SAILOR 2009[39]						Yes
1169	0.3 mg	4.6±1.7	12	79	81.4	
1209	0.5 mg	4.6±1.7	12	79	82.0	
CATT2011[41]						No
301	0.5 mg	12	12	79	93	
298	0.5 mg	6.9±3.0	12	78	93	
EXCITE 2011[40]						Yes
120	0.3 mg	6	12	75	88.3	
118	0.5 mg	6	12	76	80.5	
115	0.3 mg	12	12	75	89.6	
IVAN 2012[43]						No*
157	0.5 mg	12.2±1.6	12	78	98.2	
155	0.5 mg	7.5±2.9	12	78	98.2	
DENALI 2012[42]						Yes
210	0.5 mg + PDT	5.5	12	77	89.1	
111	0.5 mg	10.6	12	77	89.1	
EVEREST 2012[34]						Yes
21	PDT	0	6	62	96.7	
19	0.5 mg + PDT	3.9	6	64	96.7	
21	0.5 mg	5.2	6	69	96.7	
HARBOR 2013[44]						Yes
274	0.5 mg	11.3±1.8	12	79	94.5	
275	0.5 mg	7.7±2.7	12	79	94.5	
274	2.0 mg	11.2±2.1	12	79	94.5	
272	2.0 mg	6.9±2.4	12	78	94.5	

PDT = photodynamic therapy.
*The principal investigators and their hospital had financial relationships with the manufacturer.

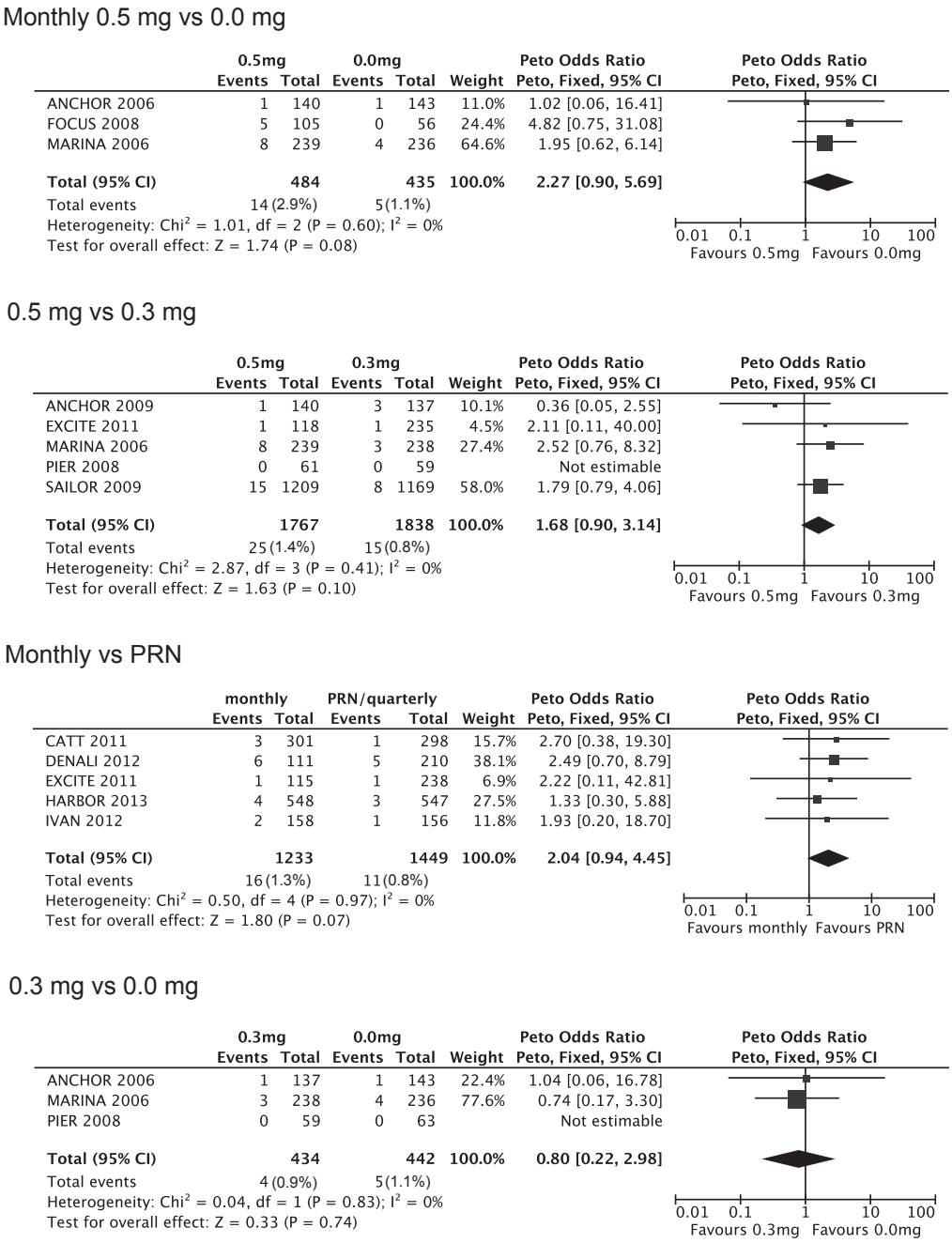

Figure 2. Ranibizumab and cerebrovascular accidents: comparisons between different regimen categories. CI = confidence interval; PRN = pro re nata.

Selection Criteria

We screened all retrieved publications according to predefined eligibility criteria for inclusion in this analysis. Eligible studies were exclusively randomized trials that compared different intensities of ranibizumab treatment for AMD and reported the incidence of CVAs, myocardial infarction (MI), nonocular hemorrhage, overall arterial thromboembolic events (ATEs), and/or all-cause mortality during the respective trial periods. We evaluated the intensity of ranibizumab treatment in terms of dose per injection as well as retreatment frequency. Regarding the dose per injection, we included studies that compared different doses of ranibizumab (0.0, 0.3, or 0.5 mg). In contrast, regarding retreatment frequency, we categorized the various frequencies into the following 3 groups: Monthly, less frequent (i.e., pro re nata [PRN] or quarterly), and no active ranibizumab treatment. We then included studies that compared different categories of re-treatment frequency. In some trials, the regimens were switched or crossed over in the middle of the trial periods; hence, the outcome data for those patients were often not specifically reported. In such cases, we included outcome data until the regimen was changed.

Data Extraction

We extracted data regarding the study characteristics; quality, dose, and re-treatment frequency of ranibizumab; and the number of nonfatal or fatal CVAs, MIs, and nonocular hemorrhage events,

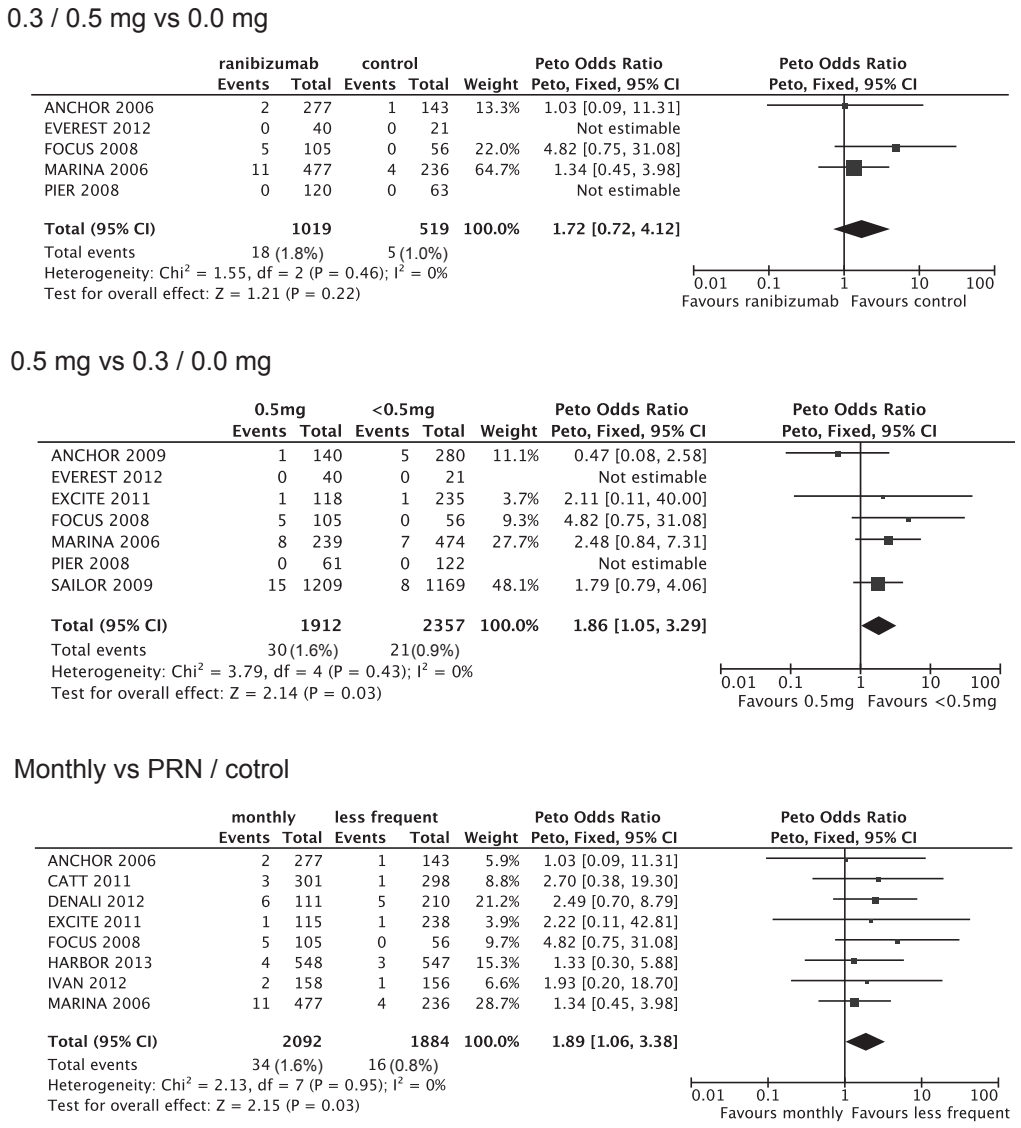

Figure 3. Ranibizumab and cerebrovascular accidents: comparisons between combined regimen categories. CI = confidence interval; PRN = pro re nata.

ATEs, and all-cause mortality. Occurrences of "myocardial infarction" and "coronary artery occlusion" were regarded as MI events. Descriptions of "stroke," "cerebral hemorrhage," "cerebral ischemic incident," "ischemic/hemorrhagic cerebrovascular conditions," and "cerebral ischemia" were regarded as CVAs. "Transient ischemic attack" was not regarded as a CVA because this diagnosis might not always be accurate. We contacted the authors of the studies for missing data. Disagreements were resolved by consensus with a third reviewer (T.Y.). If there was an inconsistency in the reported data, we referenced data available at the US FDA website (available at: www.fda.gov) because it is considered to have the most accurate data.

Qualitative Synthesis and Risk of Bias Assessment

We evaluated the clinical and methodologic characteristics as well as the strengths and limitations of the included studies using the criteria recommended by the Cochrane Collaboration[16] for the risk of bias assessment included in the sequence generation of allocation; allocation concealment; masking of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential sources of bias.

Statistical Analysis

All statistical analyses were performed in line with the recommendations of the Cochrane Collaboration. We conducted the meta-analysis using RevMan 5.2 software. Peto odds ratio (OR) with a 95% confidence interval (CI) was used to estimate the influence of ranibizumab treatment on systemic adverse events. According to the Cochrane Collaboration, the Peto OR has superior statistical properties to analyze rare events. First, we conducted a meta-analysis of all the possible comparisons between the different regimen categories, as long as there were $\geq$2 trials for which meta-analysis could be applied. However, it is often difficult to evaluate the difference in the incidence of rare events with a sufficient statistical power. For example, provided that the α and 1-β values are 0.05 and 0.9, respectively, a sample size of 790 subjects in each group is necessary to detect a 1% increase in the event that occurs at the rate of 1% in the compared group. Thus, a larger sample size is necessary to detect a smaller increase in more rare events. Therefore, we conducted a meta-analysis using a combination of regime categories, where doses of 0.3 and 0.5 mg were combined and compared with 0.0 mg (i.e., control); 0.5 mg was compared

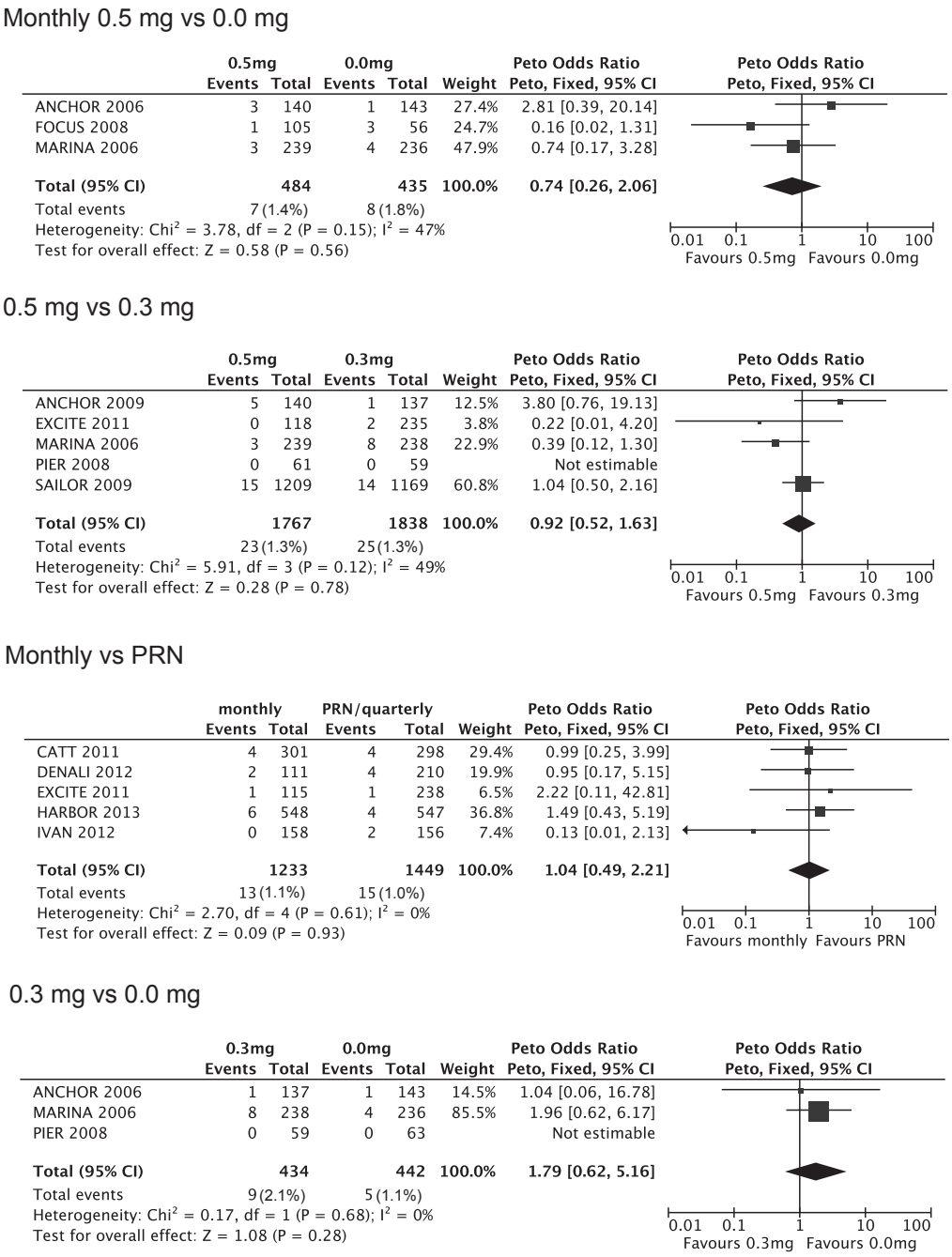

Figure 4. Ranibizumab and myocardial infarctions: comparisons between different regimen categories. CI = confidence interval; PRN = pro re nata.

with the combination of 0.3 and 0.0 mg; and monthly treatment was compared with the combination of PRN and control treatment. We assessed heterogeneity by calculating the I^2 statistic and performing chi-squared tests.

Results

Literature Search

The first database query yielded 1841 citations. After screening the titles and abstracts, we selected 31 articles as potentially relevant. Reviews of the 31 full-length articles resulted in the exclusion of 18 articles.[4,17–34] As a result, we included 11 studies with 13 published articles.[2,3,34–44] A flow chart of the selection process is provided in Figure 1. Of note, in one of the included trials,[3,35] 35% of the patients in the control group were switched from 0.0 to 0.3 mg of ranibizumab during the second year. Therefore, we used either 1- or 2-year reports, depending on the analysis.

Qualitative Synthesis

The characteristics of the included studies are presented in Table 1. All 11 studies included in this meta-analysis were prospective,

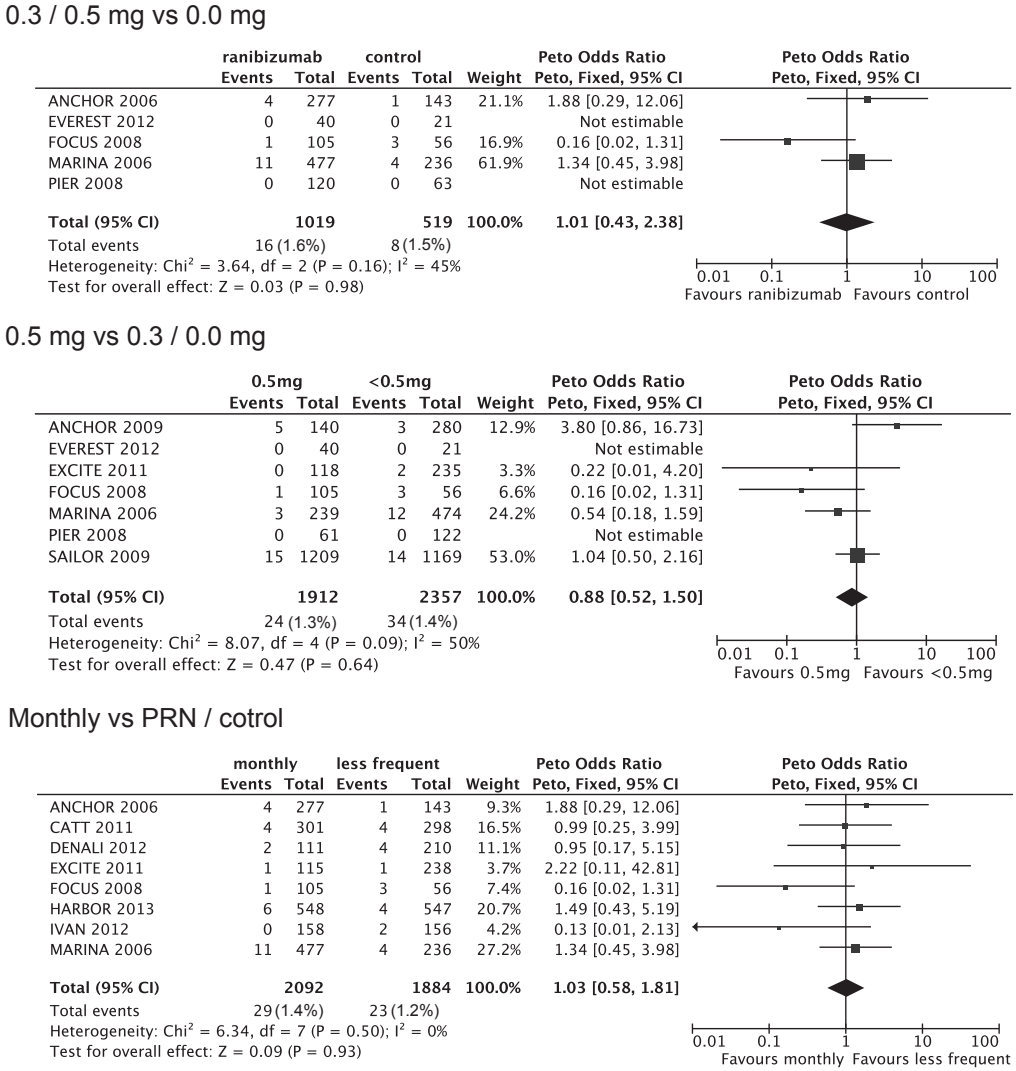

Figure 5. Ranibizumab and myocardial infarctions: comparisons between combined regimen categories. CI = confidence interval.

multicenter, randomized trials with follow-up completion rates of >80%. Only 1 of the 11 trials[41] was conducted independent of support from a drug manufacturer or without a declared conflict of interest. Eight studies[2,3,34,38,40–42,44] were double-masked (i.e., patients and outcome assessors) and 2 studies[37,39] were single-masked trials. In 1 trial,[43] neither the patients nor investigators were masked to the ranibizumab regimens. For randomized trials, adverse events are recorded using terms from the *Medical Dictionary for Regulatory Activities* (MedDRA). Antiplatelet Trialists' Collaboration criteria were sometimes used to select more severe events from the MedDRA-based events. In the trials included for the present meta-analysis, 6 studies[34,36,37,40-43] used the MedDRA-preferred terms to describe the outcome data, whereas the other 5 trials[2,3,35,38,39,44] used the Antiplatelet Trialists' Collaboration criteria. As is typical for patients with AMD, the patients were elderly in most trials (mean age, >75 years). The range of the observation periods was 6 to 24 months among the included studies. Five trials[2,3,34,35,36,37,38] compared ranibizumab to control treatments (i.e., sham injection or photodynamic therapy [PDT]), whereas the other 6 studies[39,40,41,42,43,44] compared different dosages and frequencies of ranibizumab. None of the 11 trials indicated a significant increase in systemic adverse events. In a phase IIIb trial[39] that primarily evaluated safety, a significant increase in the incidence of CVAs in patients treated with 0.5 mg of ranibizumab compared with those treated with 0.3 mg was observed until an interim analysis at 6 months.[5] However, the significant difference disappeared by 12 months. In 1 trial,[3,35] the number of reported CVAs was inconsistent between the 1- and 2-year reports.[3,35] Because the 1-year report was published in the highest-quality journal and the number of CVAs was also recorded by the FDA,[45] the number of CVAs was included in the present meta-analysis after discussion with the third reviewer (Y.T.).

Risk of Bias Assessment

Two studies[2,38] were judged to have a low risk of bias in all assessment categories. The other 9 studies were considered to have some risk of bias because of unclear descriptions of random sequence generation, allocation concealment, and/or masking procedures (Table 2; available at www.aaojournal.org).

Ranibizumab and CVAs

The meta-analysis results of comparisons between different regimen categories are shown in Figure 2. There was a nonsignificant increase of CVAs in the regimens of 0.5 versus 0.0 mg (OR, 2.27; 95% CI, 0.90−5.69; $P = 0.08$), 0.5 versus 0.3 mg (OR, 1.79; 95% CI, 0.79−4.06; $P = 0.10$), and monthly

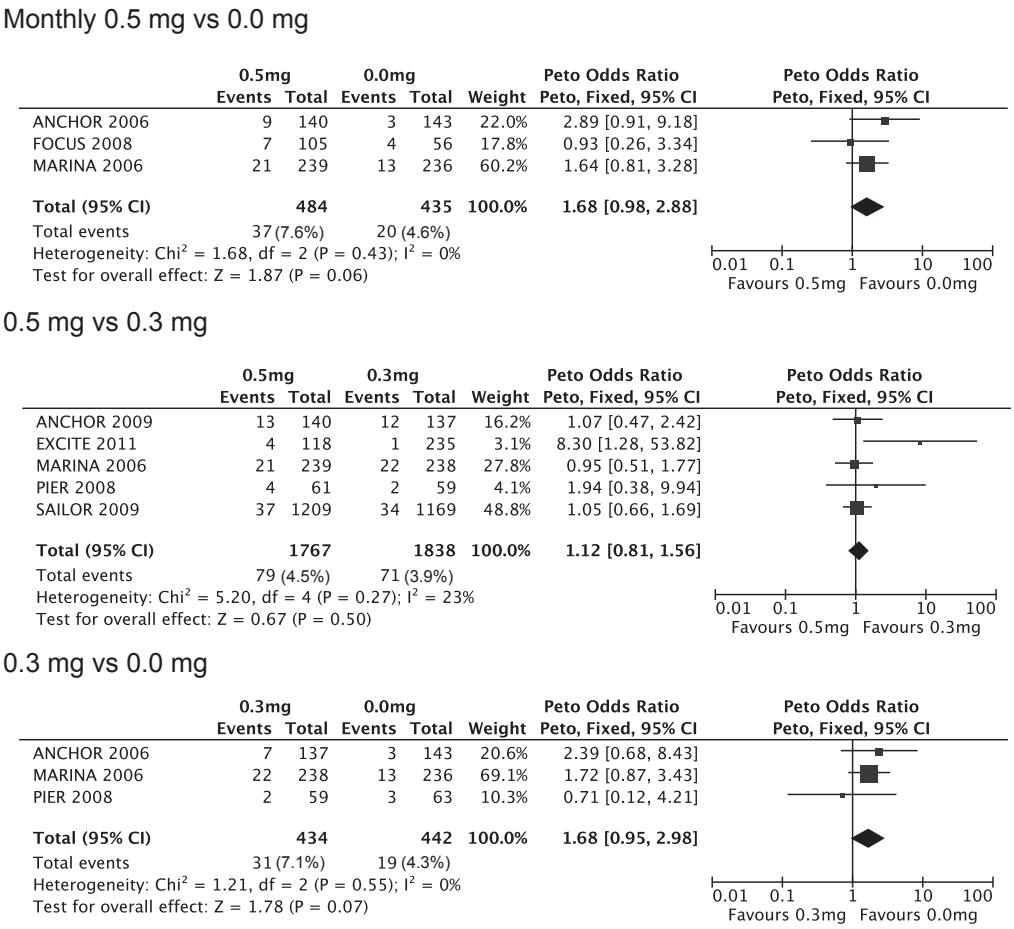

Figure 6. Ranibizumab and nonocular hemorrhage: comparisons between different regimen categories. CI = confidence interval.

treatment compared with PRN treatment (OR, 2.04; 95% CI, 0.94−4.45; $P = 0.07$). There was no apparent difference in the influence of treatment with 0.3 mg ranibizumab compared with no ranibizumab (OR, 0.80; 95% CI, 0.22−2.98; $P = 0.74$). The meta-analysis results of comparisons between combined regimen categories are shown in Figure 3. When we compared the combination of the 0.3 and 0.5 mg groups with the no ranibizumab group, the influence was not significant (OR, 1.72; 95% CI, 0.72−4.12; $P = 0.22$). On the other hand, the influence of 0.5 mg compared with the combination of 0.3 mg and no ranibizumab groups was significant (OR, 1.86; 95% CI, 1.05−3.29; $P = 0.03$). In addition, when the monthly treatment group was compared with the combined PRN and no ranibizumab groups, we observed a significant increase in the number of CVAs (OR, 1.89; 95% CI, 1.06−3.38; $P = 0.03$).

Ranibizumab and Myocardial Infarction

The meta-analysis results of comparisons between the different regimen categories are shown in Figure 4. There was no apparent influence of ranibizumab in the comparisons of 0.5 versus 0.0 mg (OR, 0.74; 95% CI, 0.26−2.06; $P = 0.56$), 0.5 versus 0.3 mg (OR, 0.92; 95% CI, 0.52−1.63; $P = 0.78$), monthly versus PRN (OR, 1.04; 95% CI, 0.49−2.21; $P = 0.93$), or 0.3 versus 0.0 mg (OR, 1.79; 95% CI, 0.62−5.16; $P = 0.28$). Similarly, for the comparisons between combined regimen categories (Fig 5), the OR (95% CI) for 0.3/0.5 versus 0.0 mg, 0.5 versus 0.3/0.0 mg, and monthly versus PRN/control treatments were 1.01 (0.43−2.38), 0.88 (0.52−1.50), and 1.03 (0.58−1.81), respectively.

Ranibizumab and Nonocular Hemorrhage

Comparisons between treatment categories (Fig 6) revealed a nonsignificant increase in the number of nonocular hemorrhage events in 0.5 versus 0.0 mg treatment regimens (OR, 1.68; 95% CI, 0.98−2.88; $P = 0.06$) and 0.3 versus 0.0 mg (OR, 1.68; 95% CI, 0.95−2.98; $P = 0.07$). The meta-analysis results using the combined categories (Fig 7) revealed a significant difference for the comparison of 0.3/0.5 mg with no ranibizumab (OR, 1.57; 95% CI, 1.01−2.44; $P = 0.04$), whereas the meta-analysis of 0.5 versus 0.3/0.0 mg (OR, 1.24; 95% CI, 0.91−1.68; $P = 0.18$) and monthly versus PRN/control (OR, 1.54; 95% CI, 0.98−2.42; $P = 0.06$) did not show a difference.

Ranibizumab and Overall Arterial Thromboembolic Event

The meta-analysis results of comparisons between each regimen category and those between combined regimen categories are shown in Figs 8 and 9, respectively (available at www.aaojournal.org). The meta-analysis indicated a nonsignificant increase in monthly treatment compared with PRN (OR, 1.58; 95% CI, 0.96−2.61; $P = 0.07$) and monthly treatment compared with PRN/control (OR, 1.42; 95% CI, 0.99−2.05; $P = 0.06$). In contrast, there was no apparent difference in ATE risk among regimens using different doses.

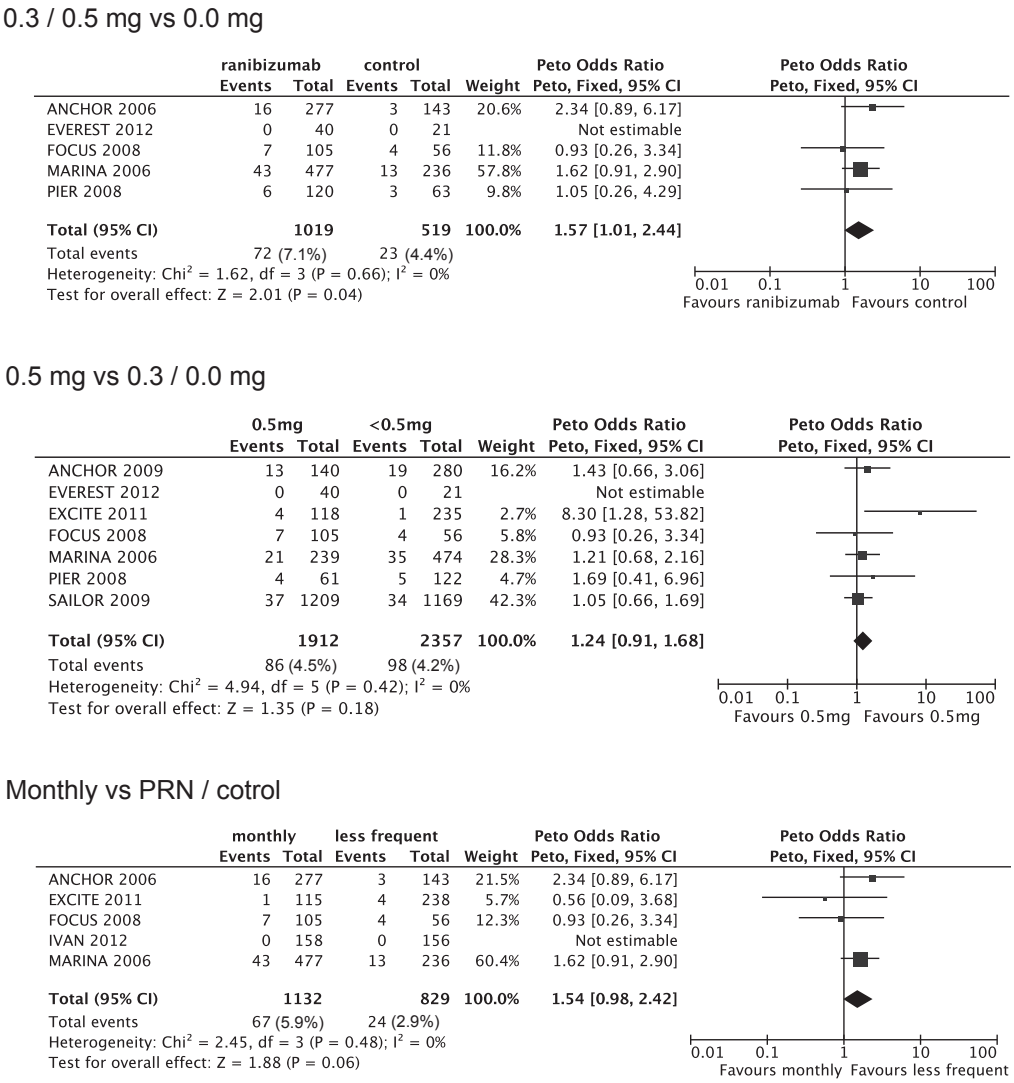

Figure 7. Ranibizumab and nonocular hemorrhage: comparisons between combined regimen categories. CI = confidence interval; df = degree of freedom; PRN = pro re nata.

Ranibizumab and All-cause Mortality

The results of our meta-analysis confirmed that ranibizumab treatment for AMD did not influence the overall risk of mortality (Figs 10 and 11; available at www.aaojournal.org).

Table 3. Studies of Ranibizumab for Age-related Macular Degeneration Included in Previous Meta-analyses to Evaluate Systemic Vascular Safety

Reference	No. of Patients	Study Names
Ueta 2009[6]	3	MARINA, ANCHOR, FOCUS
Schmucker 2011[13]	3	MARINA, ANCHOR, PIER
Schmucker 2012[14]	5	MARINA, ANCHOR, PIER, SAILOR, EXCITE
Cheng 2012[15]	4	MARINA, ANCHOR, FOCUS, PIER
This report	11	MARINA, ANCHOR, FOCUS, PIER, SAILOR, EXCITE, CATT, EVEREST, DENALI, IVAN, HARBOR

Sensitivity Analyses

Herein we have reported the findings of all possible comparisons between single and combined treatment categories. In addition, we performed a meta-analysis of the assumption that all participants with incomplete records did not experience systemic adverse events. Likewise, we assigned 1 patient[2] to the no ranibizumab group, although the patient actually received 1 injection of ranibizumab by mistake and experienced a CVA 8 months later. By excluding the patient from the meta-analysis because of the apparent protocol violation, the following comparisons became significant: 0.5 versus 0.0 mg for CVA (OR, 2.66; 95% CI, 1.03−6.85; $P = 0.04$) and monthly versus PRN/control for ATEs (OR, 1.46; 95% CI, 1.01−2.10, $P = 0.04$). There were no changes in statistical significance among the remaining comparisons.

Discussion

The results of the present meta-analyses show that intravitreal ranibizumab, as a treatment for AMD, did not affect

overall mortality; however, more intensive ranibizumab treatment may increase the risk of CVAs, nonocular hemorrhage, or ATEs. Moreover, these findings present a dilemma because an 0.5-mg dose of ranibizumab is the most commonly used in clinical practice, and frequent retreatment is often necessary to maintain visual acuity in some patients. In addition, the 0.5-mg dose used for intravitreal ranibizumab injection is small compared with that of the intravenously administered VEGF inhibitors. Nonetheless, our meta-analysis results suggest that even a small antiangiogenic insult may produce an effect in patients with exudative AMD. This may be related to the fact that cerebrovascular integrity becomes considerably more vulnerable after the age of 75.[46] The increased number of CVAs, but not of MIs, may be attributable to the anatomic closeness of the vitreous cavity to the subarachnoid space. Therefore, future studies to discern the mechanisms of how intravitreal ranibizumab affects the cerebrovasculature are warranted.

In our previous report of a small meta-analysis conducted in 2009,[6] the incidence of CVA significantly increased in patients treated with monthly injections of either 0.3 or 0.5 mg of ranibizumab compared with that of patients treated with sham injections or PDT. In the same report, the risk of MI was unaffected by ranibizumab treatment, which is consistent with the results of the present study. In 2012, a pooled analysis of the initial pivotal randomized controlled trials stratified by the grades of baseline stroke risk was reported.[7] The report indicated that 0.5 mg of ranibizumab further increased the risk of stroke (OR, 7.7) compared with either a sham injection or PDT in high-risk patients. However, the relatively small sample size with a wide CI range for the subcategory analysis (n = 289) was not considered sufficiently persuasive.

There have been several retrospective, population-based studies in the setting of nonrandomized, postmarketing surveys. In one such study based on data from the US Medicare program,[9] the incidence of stroke did not increase in AMD patients treated with ranibizumab. However, the incidence of mortality and MI was lower in AMD patients treated with ranibizumab than in those treated with PDT. However, this finding was difficult to explain, and the possible serious influence of other confounders may also have played a pivotal role.[47] The other 2 studies consisted of a nested case−control study[10] and a time-series analysis.[11] In these studies, the incidence of ischemic stroke did not increase because of ranibizumab or bevacizumab treatment for retinal disorders. Limitations of these retrospective studies include that the intensity of treatment with VEGF inhibitors was not taken into account and that unexpected confounders could not be ruled out.

A list of studies of ranibizumab treatment for AMD that were included in previous meta-analyses to evaluate systemic vascular safety is presented in Table 3. Notably, there were fewer studies included in these previous meta-analyses, and some reports[13,14] did not specifically address cerebrovascular and cardiovascular risks. Another report[15] assessed studies of bevacizumab and pegaptanib for diabetic macular edema and retinal vein occlusions together with those of ranibizumab for AMD. However, it is difficult to include studies of different disorders with different backgrounds treated with different VEGF inhibitors in the same meta-analysis without adjusting for various confounders.

The present meta-analysis had several limitations. First, although we categorized the study groups based on the dose and frequency of ranibizumab injections, there was still some variation among the PRN treatment regimens. In addition, there was a difference in the follow-up periods among the included studies. Second, only 1 of the 11 included studies was independent of support of a drug manufacturer or a conflict of interest. The influence of industry sponsorship on research outcomes has been previously discussed as a possible source of bias.[48−50] Third, although safety evaluation was a specific aim of all the included trials, randomized trials are sometimes not suitable to evaluate rare adverse events, and postmarketing studies may provide useful information regarding safety issues. Fourth, the Peto OR is suitable for meta-analysis of rare events. Although the minority of study arms have unequal size, the influence is considered to be small.

In conclusion, the results of the present systematic review and meta-analysis suggest that intravitreal ranibizumab treatment for AMD could produce systemic adverse vascular effects, although there was no noticeable impact on the risk of mortality. In addition, the results of this meta-analysis provide a basis for other safety issues under debate, including comparisons between ranibizumab and bevacizumab[30,41,43] as well as ranibizumab and aflibercept.[51,52]

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Footnotes and Financial Disclosures

Originally received: May 13, 2013.
Final revision: May 21, 2014.
Accepted: May 21, 2014.
Available online: July 12, 2014. Manuscript no. 2013-771.

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Financial Disclosures:
The authors have made the following disclosures:

Shiro Amano − Lecturer − Santen Pharmaceutical, Senju Pharmaceutical, Alcon, Merck Sharp & Dohme, Otsuka Pharmaceutical, Novartis Pharma, Abbott Medical Optics, HOYA.

The sponsors and funding agencies were not involved in the design or execution of this review or interpretation of the results. No drug manufacturing company was involved in the study design, data collection, analysis, and interpretation, writing of the report, or decision to submit this report for publication.

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **ATE** = arterial thromboembolic event; **CVA** = cerebrovascular accident; **FDA** = US Food and Drug Administration; **MedDRA** = Medical Dictionary for Regulatory Activities; **MI** = myocardial infarction; **OR** = odds ratio; **PDT** = photodynamic therapy; **PRN** = pro re nata (as needed); **VEGF** = vascular endothelial growth factor.

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Protocol

Systemic Vascular Safety of Ranibizumab for Age-related Macular Degeneration: Systematic Review and Meta-analysis of Randomized Trials

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***Background*:** Vascular endothelial growth factor (VEGF) inhibitors have drastically changed the way to treat exudative age-related macular degeneration (AMD) since the appearance of ranibizumab in 2006.[1,2] Ranibizumab is a VEGF inhibitor that has been most intensively evaluated in various randomized trials. Other VEGF inhibitors including off-label bevacizumab and recently introduced aflibercept have established their usefulness in comparison with ranibizumab. Despite the unquestionable effectiveness, the increased risk of systemic vascular events has been hotly discussed but remained unclear.[3-6]

Ranibizumab has also been tested for other pathologies including diabetic macular edema and retinal vein occlusion through phase III randomized trials. In those trials patients with high risk for systemic vascular events were excluded from the trials.[8-12] In contrast, in most of the trials for AMD, there has been no exclusion criterion for systemic vascular conditions. However, considering that a majority of patients with exudative AMD is considerably old (>75 years old), intensive treatment with ranibizumab might lead to increased systemic vascular risks. In that case we may also need to take systemic vascular risks into account to treat AMD patients with VEGF inhibitors.

Review Objectives: To conduct a meta-analysis of randomized trials of ranibizumab for AMD and assess whether ranibizumab treatment affects the systemic vascular risk or mortality.

Methods: The study will be conducted according to the PRISMA statement and will be reported according to the PRISMA reporting guideline.

Population

Patients with exudative AMD participating in randomized trials published in peer-reviewed journals in which the relevant outcomes were analyzed.

Selection Criteria

Inclusion criteria (all of the following must be true)

- Original reports (primary data collection) of randomized trials, regardless of the number of participants and follow-up period, with or without exclusion of participants due to systemic vascular conditions at baseline.
- Studies comparing different intensities of ranibizumab treatment for AMD in terms of dose per injection and retreatment frequency including control sham injection.
- Studies reporting the number of systemic adverse events including cerebrovascular accident (CVA), myocardial infarction (MI), nonocular hemorrhage, arterial thromboembolic event (ATE), and/or overall mortality.

Exclusion criteria

- Studies in which safety data for the specific regimen of ranibizumab are not available.
- Concomitant use of other drugs that also have an anti-VEGF effect.

Database search

MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials will be used with the following search strategy.

1. exp macular degeneration/
2. (macular adj6 degeneration).mp.
3. exp choroidal neovascularization/
4. (choroidal adj6 neovascularization).mp.
5. 1 or 2 or 3 or 4
6. ranibizumab.mp.
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized.ab.
10. placebo.ab.
11. drug therapy.fs.
12. randomly.ab.
13. trial.ab.
14. groups.ab.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 5 and 6 and 15

Preliminary independent screening of the titles ad abstracts obtained from the database searches will be carried out by two researchers (T.U. and T.T.). This step will be carried out to remove obviously irrelevant articles. Because it is often difficult to find out whether the articles have safety data that satisfy selection criteria based on only the titles and abstracts, all reports will be included as long as they are randomized trials of ranibizumab for

AMD. Then the screened articles will be examined for their eligibility based on a full review of the article. Any disagreements at any of the screening stages will be resolved by discussion between the two reviewers in the first instance. If agreement cannot be reached, then a third reviewer (T.Y.) will independently review the title, abstract, or full article, as appropriate, and a majority decision will be made on inclusion/exclusion.

Hand searches

To ensure that we have a complete list of articles relevant to our research question, we will conduct hand-searches through the reference lists of the articles included in our review and published systematic reviews.

Languages

No language restriction for the inclusion of relevant studies.

Data extraction

Study characteristics

Data relating to study names, design, year of publication, the number of participants, the mean age, regimens of ranibizumab including dose and retreatment frequency, follow-up period, completion rate of follow-up, support from manufactures, and existence of exclusion criteria as for baseline systemic vascular conditions will be extracted. For this purpose, data at ClinicalTrials.gov and FDA.gov will be used in addition to published data. Authors of the trials will be contacted for missing data.

Study quality

As recommended by Cochrane Collaboration, risk of bias will be assessed based on the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Because the injection of active drug requires puncturing the eye with needles, whereas sham injection does not require puncture, the physicians who administer the injection cannot be blinded. In that case, the evaluating physician should be blinded for the patients' treatment assignment for proper blinding. Blinding of other personnel and patients is also necessary for the completion of double blinding.

Outcome data

- Interventions and comparators
  Intravitreal injection of ranibizumab with different doses and frequencies, including sham injection, will be compared. Photodynamic therapy is not considered to influence the risk of systemic vascular events.
- Outcome measures
  The number of events for CVA, MI, nonocular hemorrhage, ATE, and overall death.

Meta-analysis

Peto odds ratio will be used to estimate the risk ratio with 95% confidence interval. Heterogeneity will be tested by calculating the I^2 statistic. Treatment regimens will be categorized based on the intensities of ranibizumab treatment: 0.5, 0.3, and 0.0 mg (no active treatment); monthly retreatment; and less frequent retreatment. From a clinical viewpoint where frequent injections of 0.5 mg ranibizumab are often necessary to maintain good visual acuity, the meta-analysis will especially focus on the safety of intensive treatment (i.e., 0.5 mg and/or monthly treatment) compared with other less intensive treatment including no active treatment. This grouping will confer statistical power by maximizing the number of patients included in the meta-analysis. However, meta-analysis comparing each category of regimen will also be conducted. As for missing data, analysis will be conducted according to intension-to-treat (ITT) basis. Participants who violated protocols (e.g., participants who were treated by mistake) will also be analyzed on an ITT basis, but their exclusion will be tested in a sensitivity analysis.

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Table 2. Risk of Bias Assessment

	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of Participants and Personnel (performance bias)	Blinding of Outcome Assessment (detection bias)	Incomplete Outcome Data (attrition bias)	Selective Reporting (reporting bias)	Other bias
MARINA 2006[2]	L	L	L	L	L	L	L
FOCUS 2008[36,37]	U	H	H	L	L	L	L
PIER 2008[38]	L	L	L	L	L	L	L
ANCHOR 2006, 2009[3,35]	U	U	L	L	L	L	L
SAILOR 2009[39]	U	U	H	H	L	L	L
CATT 2011[41]	L	L	L	H	L	L	L
EXCITE 2011[40]	U	U	L	L	L	L	L
IVAN 2012[43]	L	L	H	H	L	L	L
DENALI 2012[42]	U	U	L	L	L	L	L
EVEREST 2012[34]	U	U	L	L	L	L	L
HARBOR 2013[44]	L	L	H	L	L	L	L

H = high risk; L = low risk; U = unclear risk.

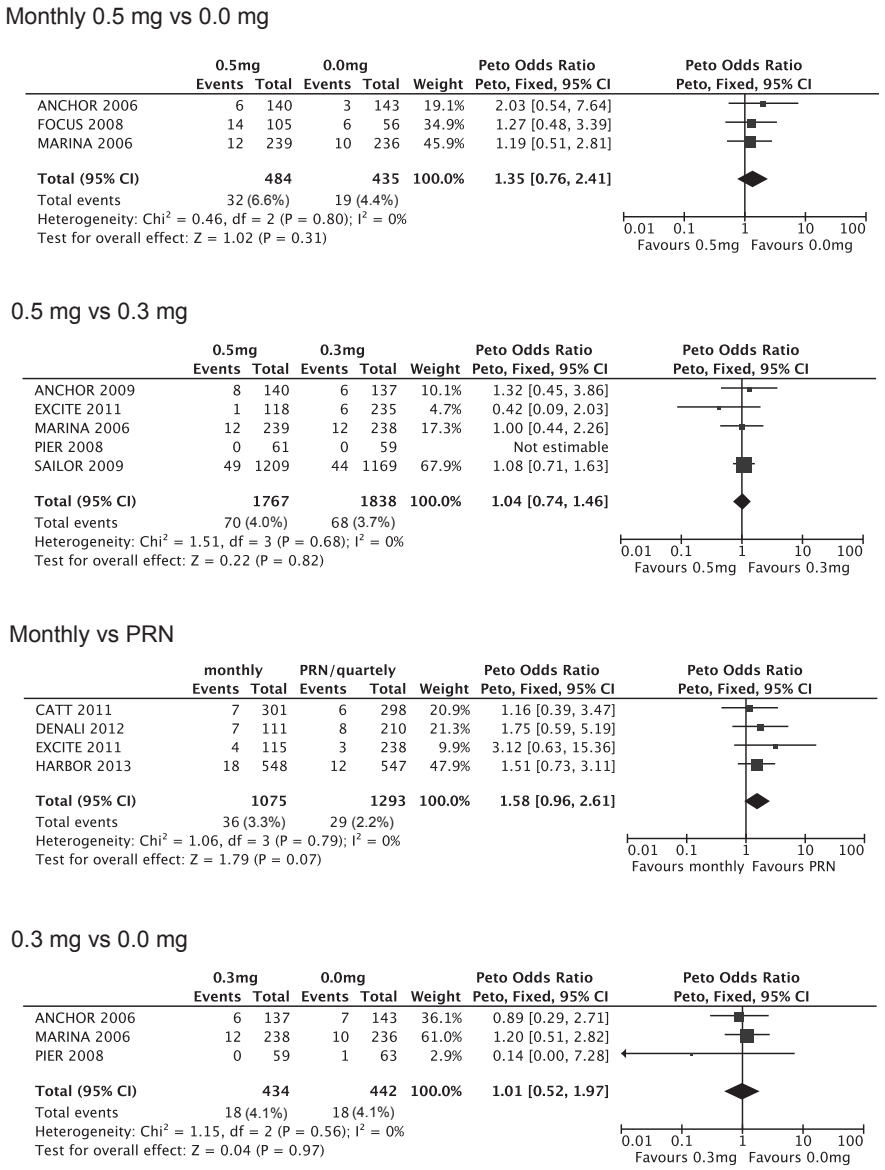

Figure 8. Ranibizumab and overall arterial thromboembolic events: comparisons between different regimen categories. CI = confidence interval; PRN = pro re nata.

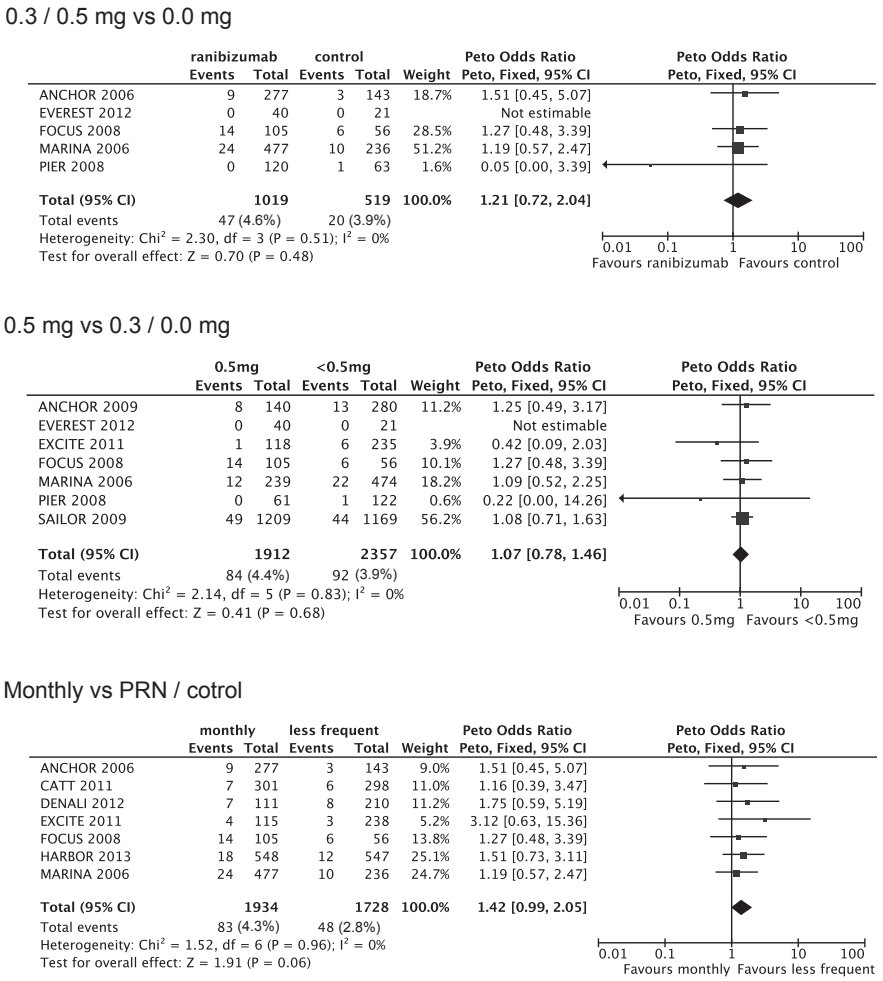

Figure 9. Ranibizumab and overall arterial thromboembolic events: comparisons between combined regimen categories. CI = confidence interval; PRN = pro re nata.

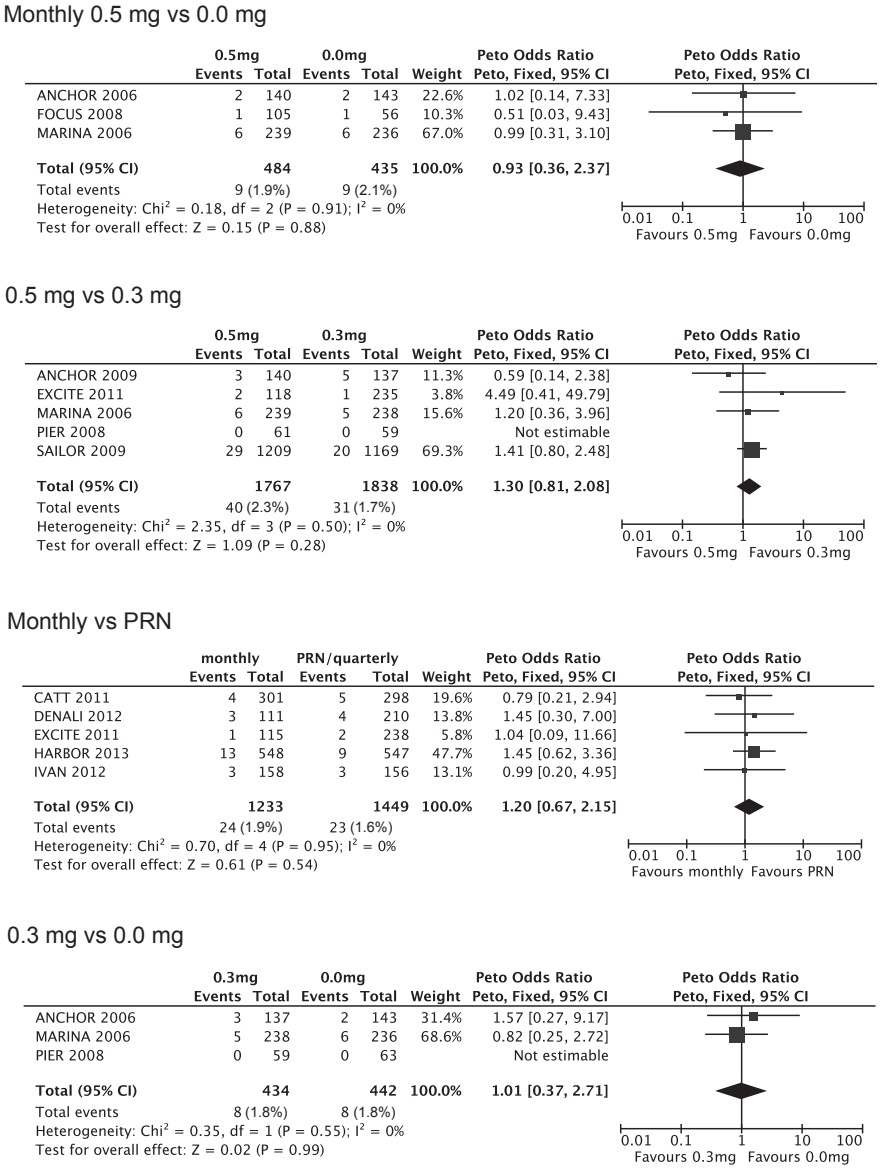

Figure 10. Ranibizumab and all-cause mortality: comparisons between different regimen categories. CI = confidence interval; PRN = pro re nata.

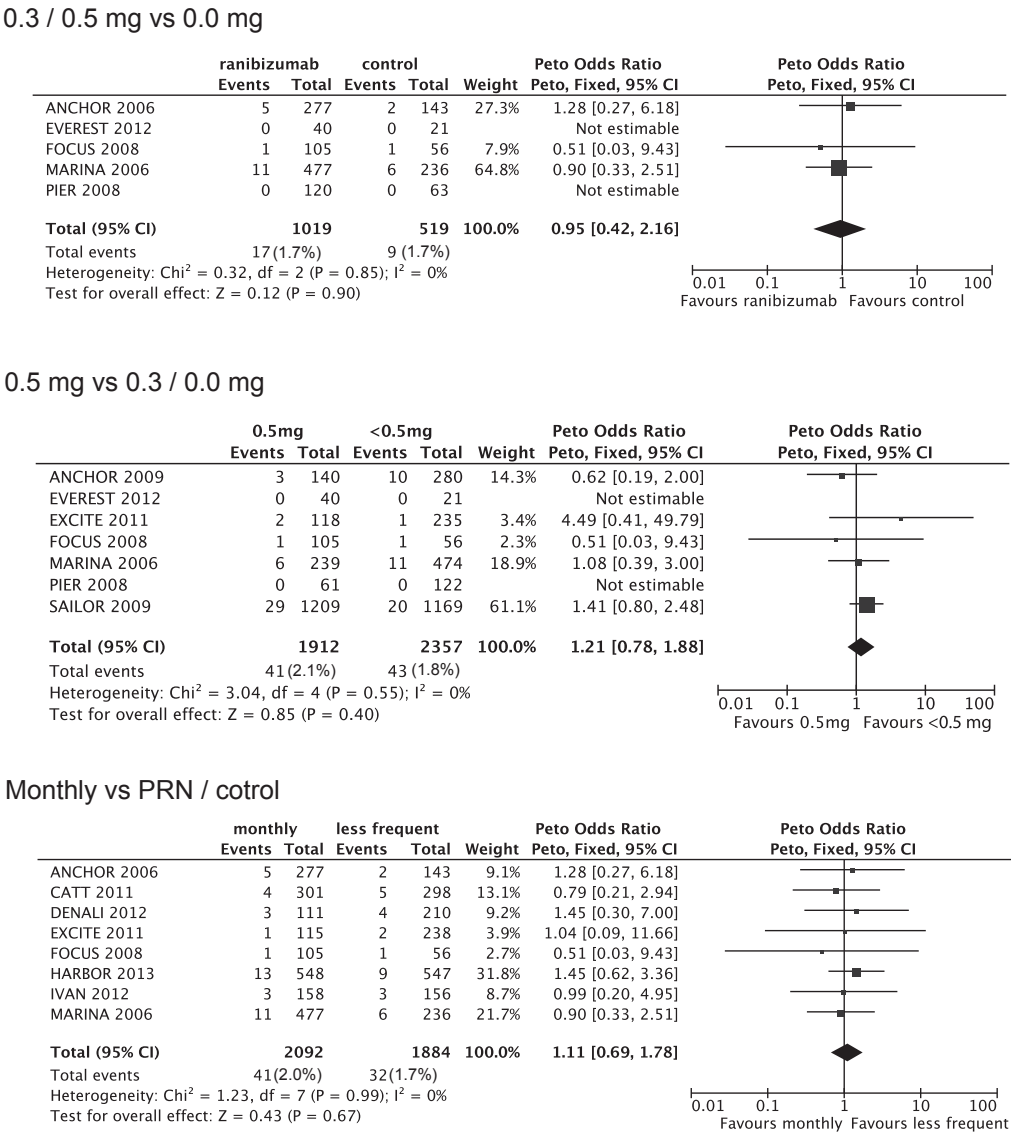

Figure 11. Ranibizumab and all-cause mortality: comparisons between combined regimen categories. CI = confidence interval; PRN = pro re nata.