AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Systemic Safety in Ranibizumab-Treated Patients with Neovascular Age-Related Macular Degeneration: A Patient-Level Pooled Analysis

Marco A. Zarbin, MD, PhD,[1] Steven Francom, PhD,[2] Susanna Grzeschik, PhD, RPh,[2] Lisa Tuomi, PharmD,[2] Zdenka Haskova, MD, PhD,[2] Wayne Macfadden, MD,[3] Philippe Margaron, PhD,[3] Howard Snow, MBBS,[3] Alan Cruess, MD,[4] Giovanni Staurenghi, MD,[5] Cornelia Dunger-Baldauf, PhD[3]

Topic: This study evaluated the cardiovascular/cerebrovascular safety profile of ranibizumab 0.5 mg versus sham ± verteporfin in patients with neovascular age-related macular degeneration (nAMD). In addition, comparisons of ranibizumab 0.3 mg with sham and ranibizumab 0.5 mg to 0.3 mg were performed.

Clinical Relevance: Intravitreal anti–vascular endothelial growth factor (VEGF) agents carry potential increased systemic risks, including cardiovascular or cerebrovascular events. Pooled safety analyses allow better interpretation of safety outcomes seen in individual clinical trials, especially for less common events. To our knowledge, this is the largest patient-level pooled analysis of patients with nAMD treated with ranibizumab.

Methods: Patient-level pooled analysis of data from 7 Genentech- and Novartis-sponsored phase II, III, and IV studies in nAMD that were completed by December 31, 2013. Pairwise comparisons (primary comparison: ranibizumab 0.5 mg [globally approved dose for nAMD] vs. sham or verteporfin) were performed using Cox proportional hazard regression (hazard ratios [HRs], 95% confidence intervals [CIs]) and rates per 100 patient-years. Standardized Medical Dictionary for Regulatory Activities queries (SMQs) and extended searches were used to identify relevant safety endpoints, including arterial thromboembolic events (ATEs), myocardial infarction (MI), stroke or transient ischemic attack (TIA), stroke (excluding TIA), vascular deaths, and major vascular events as defined by the Antiplatelet Trialists' Collaboration (APTC).

Results: The HRs (95% CIs) for the primary comparison of ranibizumab 0.5 mg (n=480) versus sham or verteporfin (n=462) were 1.16 (0.72–1.88) for ATE, 1.33 (0.59–2.97) for MI, 1.43 (0.54–3.77) for stroke excluding TIA, 1.25 (0.61–2.55) for stroke or TIA, 0.57 (0.18–1.78) for vascular death, and 1.12 (0.64–1.98) for APTC events. Hazard ratio 95% CIs included 1, indicating no significant treatment differences, for all endpoints for comparison of ranibizumab 0.5 mg versus sham or verteporfin.

Conclusions: The rates of cardiovascular and cerebrovascular events were low in these patients with nAMD and not clinically meaningfully different for patients treated with ranibizumab 0.5 mg versus sham or verteporfin, which supports the favorable benefit–risk profile of ranibizumab in the patient population with nAMD. Pooling these studies allows an analysis with higher power and precision compared with individual study analyses. *Ophthalmology Retina 2018;■:1–9 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

Intravitreal anti–vascular endothelial growth factor (VEGF) agents have demonstrated safety and efficacy in large, controlled clinical trials in a number of retinal diseases, including neovascular age-related macular degeneration (nAMD), macular edema secondary to retinal vein occlusions, choroidal neovascularization secondary to pathological myopia, and diabetic eye disease, including diabetic macular edema, proliferative diabetic retinopathy, and diabetic retinopathy, in patients with diabetic macular edema. The safety and efficacy of the anti-VEGF biological agent that has been studied the most extensively, ranibizumab (Lucentis, Genentech, Inc, South San Francisco, CA; Novartis Pharma, Basel, Switzerland), have been evaluated in multiple large, randomized, controlled clinical trials across retinal vascular diseases involving VEGF, including nAMD.[1-4] Ranibizumab is an affinity-matured monoclonal antibody fragment designed for intraocular use specifically without an Fc domain, leading to a shorter systemic half-life.[5]

In studies of the anti-VEGF agent bevacizumab, a full-length antibody with an active Fc domain, an increased risk

of cardiovascular and cerebrovascular events was observed when it was administered systemically via intravenous infusions to oncology patients in much greater doses than for ophthalmic use (>5 mg/kg of body weight biweekly).[6] Intravitreal injections of ranibizumab and other anti-VEGF agents for ophthalmologic indications deliver much lower doses (0.3 mg to 0.5 mg for ranibizumab, 1.25 mg for bevacizumab,[7,8] and 2.0 mg for aflibercept,[9] not more frequently than monthly), which egress into the systemic circulation and may still have a potential for systemic safety risks.

Available data regarding a potential association between age-related macular degeneration (AMD) and cardiovascular and cerebrovascular disease are mixed.[10,11] In a diverse population of men and women aged 45 to 84 years, there were no significant differences in the rates of incident cardiovascular disease between patients with AMD and those without, although there was a higher incidence of events in patients with advanced AMD compared with those without AMD.[10] Several studies have identified an increased risk of stroke in patients with nAMD.[12-15]

Pooled safety analyses can provide more precise and accurate estimates of safety outcomes, particularly for less common adverse events (AEs), and can potentially identify features that are not apparent in individual studies. In this pooled analysis, the combination of patient-level safety data across multiple (US and global), randomized, controlled studies increases the potential to detect treatment differences for less common AEs. This pooled analysis of patient-level data also incorporates more information (e.g., patient-level baseline risk factors and timing of each individual event with respect to drug exposure) compared with most traditional meta-analyses based on published study-level data. The objective of this analysis is for Novartis and Genentech to provide the retinal community the cumulative global experience in evaluating the safety of ranibizumab by pooling results across company-sponsored clinical trials in nAMD.

Methods

A formal statistical analysis plan was prespecified before the start of this project, defining study inclusion criteria, definition of endpoints, classification of potential risk factors, and analysis methods.

Study Selection

Phase II, III, and IV randomized, double-masked studies in patients with nAMD sponsored by Genentech, Inc, or Novartis Pharma, which were designed and conducted to meet regulatory standards set by the health authorities in the relevant countries, were considered for this analysis. For inclusion in this pooled analysis, each study was required to have at least 2 of the following 3 treatment arms: ranibizumab 0.5 mg with or without adjunctive verteporfin, ranibizumab 0.3 mg with or without adjunctive verteporfin, or a sham or verteporfin arm, with a completion/cutoff date before December 31, 2013. Seven trials met these criteria: Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR),[1,2] Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA),[4] Phase IIIb, multicenter, randomized, double-masked, sham injection–controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or

without classic CNV secondary to AMD (PIER),[16,17] Safety Assessment of Intravitreous Lucentis for AMD (SAILOR),[18] Efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy (EVEREST),[19] Safety and efficacy of ranibizumab in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration (EXTEND I),[20] and Efficacy and Safety of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration (EXCITE).[21] Study of Ranibizumab Administered Monthly or on an As-needed Basis in Patients With Subfoveal Neovascular Age-related Macular Degeneration (HARBOR), a more recent study comparing ranibizumab 0.5 mg with 2.0 mg, did not meet study selection criteria because it did not include a ranibizumab 0.3-mg, sham, or verteporfin control arm.[3,22] All 7 studies were conducted in compliance with the tenets of the Declaration of Helsinki. The independent ethics committee or institutional review boards approved the studies, and all patients provided written informed consent before enrollment, which extended to the use of individual patient data for further analyses.
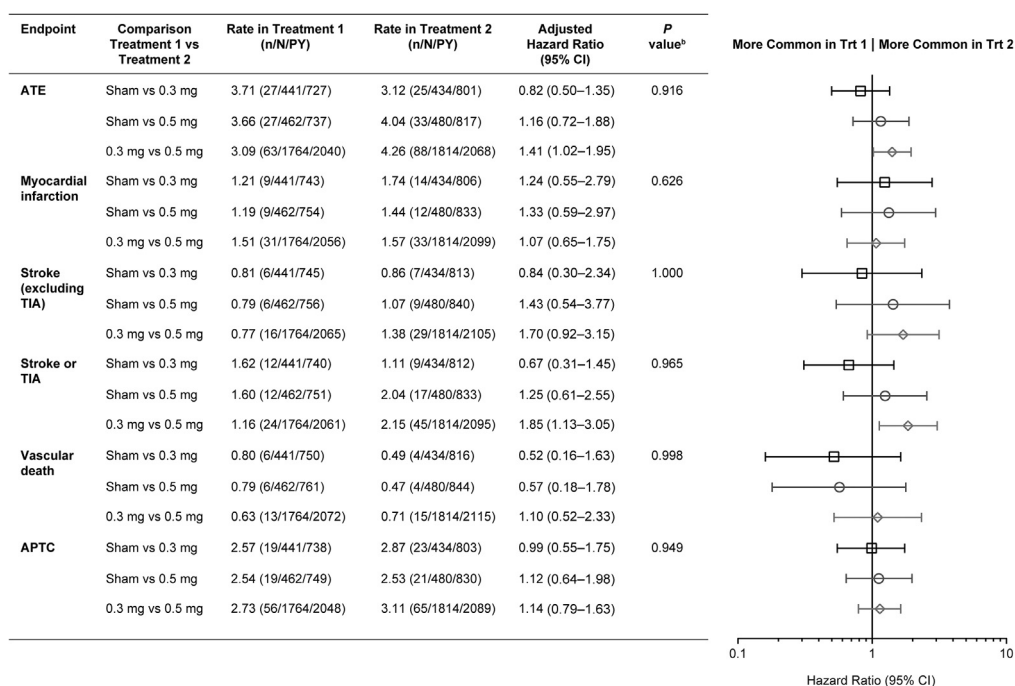
Endpoint Selection

Patient-level data available from the pooled safety database included AEs, timing of AEs, demographic data, key potential baseline risk factors obtained from patient medical history, baseline concomitant medications, and dosing information/drug exposure. The selected safety endpoints have been described previously.[23] This article's focus is on cardiovascular and cerebrovascular (arteriovascular) endpoints, which are recognized potential AEs of agents that target the VEGF pathway.[6] The analysis used Standardized Medical Dictionary for Regulatory Activities Queries (SMQs) whenever possible (Medical Dictionary for Regulatory Activities Version 16.1; Table S1, available at www.ophthalmologyretina.org). If specific SMQs were not available, the analysis used prospectively developed composite safety endpoints (based on a combination of SMQs or inclusion of a collection of preferred terms). The 6 key arteriovascular endpoints were arterial thromboembolic events (ATEs), myocardial infarction (MI), stroke or transient ischemic attack (TIA), stroke (excluding TIA), vascular death, and Antiplatelet Trialists' Collaboration (APTC) events. This analysis also evaluated other systemic events.

Pairwise Comparisons of Interventions

Patients were categorized into 3 groups based on their initial treatment: (1) ranibizumab 0.5 mg with or without verteporfin, (2) ranibizumab 0.3 mg, and (3) sham with or without verteporfin, abbreviated as (1) ranibizumab 0.5 mg, (2) ranibizumab 0.3 mg, and (3) sham in this article, respectively. The primary comparison is ranibizumab 0.5 mg versus sham because this is the approved dose for treatment of nAMD globally.[24,25] Additional comparisons include ranibizumab 0.3 mg versus sham and ranibizumab 0.5 mg versus ranibizumab 0.3 mg. To be included in a particular pairwise comparison, the individual study must have compared both treatment groups. This analysis combined studies with monthly dosing with those allowing pro re nata (PRN) or quarterly dosing.

Statistical Analysis

Only the first event was included in the analysis for patients with multiple events reported for the same endpoint; thus, for a given endpoint, each patient is only counted once. For composite endpoints such as APTC, for which a patient may have multiple events (e.g., stroke and MI), only time to the first event is included in the

Endpoint	Comparison Treatment 1 vs Treatment 2	Rate in Treatment 1 (n/N/PY)	Rate in Treatment 2 (n/N/PY)	Adjusted Hazard Ratio (95% CI)	P value[b]	More Common in Trt 1 | More Common in Trt 2
ATE	Sham vs 0.3 mg	3.71 (27/441/727)	3.12 (25/434/801)	0.82 (0.50–1.35)	0.916	
	Sham vs 0.5 mg	3.66 (27/462/737)	4.04 (33/480/817)	1.16 (0.72–1.88)		
	0.3 mg vs 0.5 mg	3.09 (63/1764/2040)	4.26 (88/1814/2068)	1.41 (1.02–1.95)		
Myocardial infarction	Sham vs 0.3 mg	1.21 (9/441/743)	1.74 (14/434/806)	1.24 (0.55–2.79)	0.626	
	Sham vs 0.5 mg	1.19 (9/462/754)	1.44 (12/480/833)	1.33 (0.59–2.97)		
	0.3 mg vs 0.5 mg	1.51 (31/1764/2056)	1.57 (33/1814/2099)	1.07 (0.65–1.75)		
Stroke (excluding TIA)	Sham vs 0.3 mg	0.81 (6/441/745)	0.86 (7/434/813)	0.84 (0.30–2.34)	1.000	
	Sham vs 0.5 mg	0.79 (6/462/756)	1.07 (9/480/840)	1.43 (0.54–3.77)		
	0.3 mg vs 0.5 mg	0.77 (16/1764/2065)	1.38 (29/1814/2105)	1.70 (0.92–3.15)		
Stroke or TIA	Sham vs 0.3 mg	1.62 (12/441/740)	1.11 (9/434/812)	0.67 (0.31–1.45)	0.965	
	Sham vs 0.5 mg	1.60 (12/462/751)	2.04 (17/480/833)	1.25 (0.61–2.55)		
	0.3 mg vs 0.5 mg	1.16 (24/1764/2061)	2.15 (45/1814/2095)	1.85 (1.13–3.05)		
Vascular death	Sham vs 0.3 mg	0.80 (6/441/750)	0.49 (4/434/816)	0.52 (0.16–1.63)	0.998	
	Sham vs 0.5 mg	0.79 (6/462/761)	0.47 (4/480/844)	0.57 (0.18–1.78)		
	0.3 mg vs 0.5 mg	0.63 (13/1764/2072)	0.71 (15/1814/2115)	1.10 (0.52–2.33)		
APTC	Sham vs 0.3 mg	2.57 (19/441/738)	2.87 (23/434/803)	0.99 (0.55–1.75)	0.949	
	Sham vs 0.5 mg	2.54 (19/462/749)	2.53 (21/480/830)	1.12 (0.64–1.98)		
	0.3 mg vs 0.5 mg	2.73 (56/1764/2048)	3.11 (65/1814/2089)	1.14 (0.79–1.63)		

Hazard Ratio (95% CI)

Figure 1. Pairwise comparisons of cardiovascular and cerebrovascular events in ranibizumab 0.5 mg, ranibizumab 0.3 mg, and sham.[a] Horizontal bars are 95% confidence intervals (CIs) of the hazard ratio (HR), reported as Trt 2 vs Trt 1. [a]Cox regression, stratified by study. [b]Interaction test for homogeneity from global Cox regression model adjusting for baseline risk factors. Numbers in the table are rates per 100 patient-years (Rate) and the number of subjects with the event (n)/number of subjects (N)/number of patient-years (PY). APTC = Antiplatelet Trialists' Collaboration; ATE = arterial thromboembolic events; TIA = transient ischemic attack; Trt = treatment.

analysis. Because of differing lengths of patient follow-up in the various studies, this analysis reports event rates for comparative purposes as rates per 100 patient-years of exposure. In addition, the percentage of patients is provided. This analysis censored sham patients who crossed over to ranibizumab therapy following the controlled portion of the studies at the time of their first ranibizumab exposure, and used the timing of each safety event relative to baseline for each patient, allowing the pooling of studies of differing durations. There were no adjustments for multiplicity.

Two modeling approaches used were: (1) separate proportional hazard Cox regression models (stratified by study), fit for each pairwise comparison and each endpoint unadjusted for baseline risk factors; and (2) global Cox regression models (stratified by study), which incorporated all pairwise comparisons adjusting for baseline risk factors (Table S2, available at www.ophthalmologyretina.org). For all models, separate and global, to assess homogeneity across studies, the study by treatment interaction term was included. Cox proportional hazard regression models allow for combining studies of different durations and incorporate the timing of each endpoint for each patient. Forest plots show study level and pooled estimates of relevant hazard ratios (HRs), 95% confidence intervals (CIs), and interaction test results. Kaplan–Meier plots show the cumulative events over time, by treatment for select endpoints.

Results

Study and Baseline Characteristics

The pooled dataset included 4080 total patients, whereas for the pairwise comparison of ranibizumab 0.5 mg versus sham, there were 480 and 462 patients, respectively (ANCHOR, MARINA, PIER,

EVEREST). For the comparison of ranibizumab 0.3 mg versus sham, there were 434 and 441 patients, respectively (ANCHOR, MARINA, PIER). For ranibizumab 0.5 mg versus 0.3 mg, there were 1814 and 1764 patients, respectively (MARINA, ANCHOR, PIER, SAILOR, EXTEND I, EXCITE). There were differing study designs, patient demographics, geographic regions, inclusion and exclusion criteria, treatment durations, ranibizumab dosing regimens, and PRN re-treatment criteria across the included studies. Overall, 426, 179, and 1249 patients were treated monthly, quarterly, and PRN in the ranibizumab 0.5 mg group; 416, 179, and 1169 patients were treated monthly, quarterly, and PRN in the ranibizumab 0.3 mg group; and 379, 62, and 21 patients were treated monthly, quarterly, and PRN in the sham group, respectively.

Cardiovascular and cerebrovascular inclusion and exclusion criteria varied among studies. ANCHOR, MARINA, and PIER (in total, 1315 [32%] of 4080 patients in the pooled data set and 94% for the primary comparison sham vs. 0.5 mg) had no specific cardiovascular or cerebrovascular exclusion criteria. EVEREST, EXTEND I, and EXCITE excluded patients with a prior cardiovascular accident (CVA). SAILOR excluded patients if cardiovascular disease was uncontrolled.[18] There was no evidence for inhomogeneity of the studies as based on study by treatment interactions (Fig 1). Generally, treatment groups were well balanced for each of the potential risk factors (Table S2, available at www.ophthalmologyretina.org).

Cardiovascular and Cerebrovascular Events

Rates of overall ATEs, MI, stroke (excluding TIA), stroke or TIA, vascular death, and APTC events were similar for both the
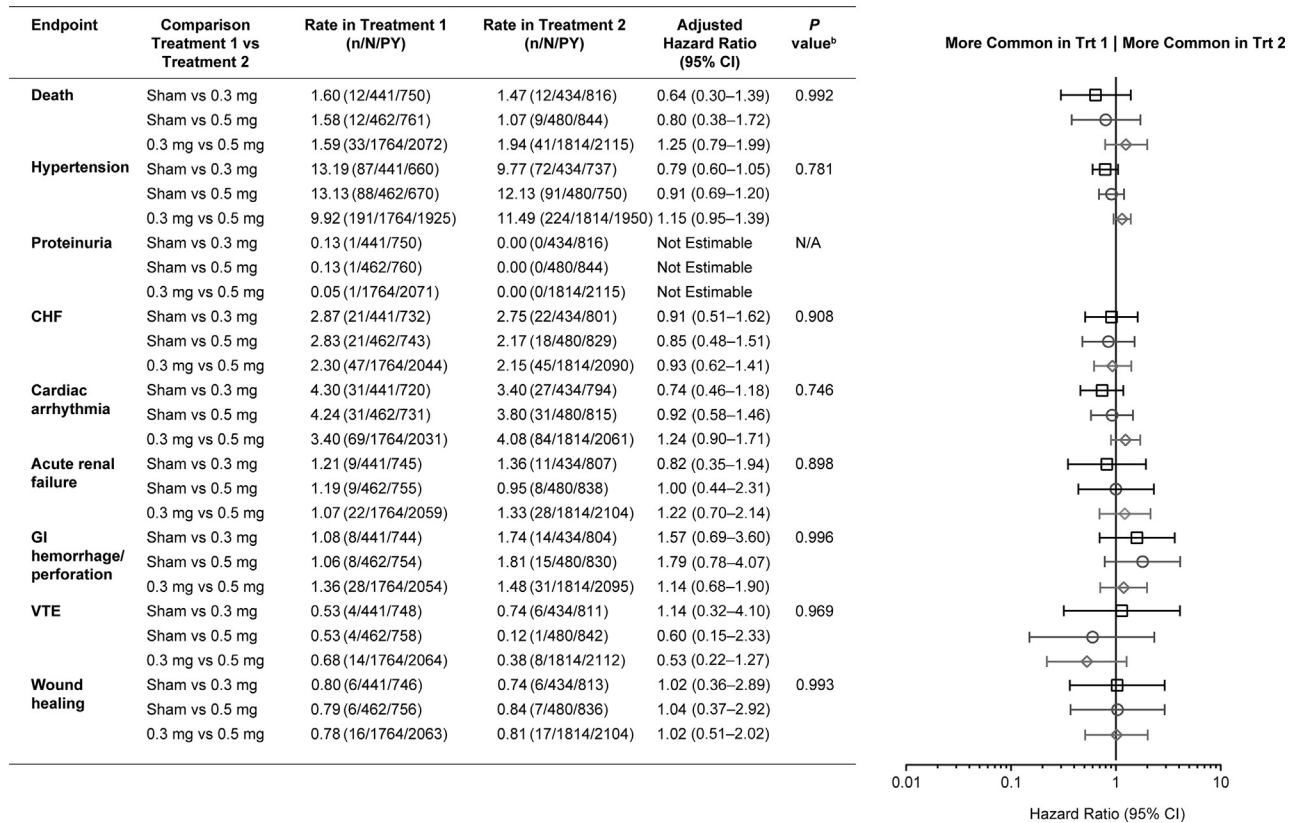
Figure 2. Pairwise comparisons by study of key cardiovascular and cerebrovascular endpoints.[a] Arterial thromboembolic events **(A)**, myocardial infarction (MI) **(B)**, stroke (excluding TIA) **(C)**, stroke or TIA **(D)**, vascular death **(E)**, and APTC **(F)** by study and overall. Horizontal bars are 95% confidence intervals (CIs) of the hazard ratio (HR), reported as Trt 2 vs Trt 1. [a]Cox regression, stratified by study. Numbers in the table are rates per 100 patient-years (Rate) and the number of subjects with the event (n)/number of subjects (N)/number of patient-years (PY). ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; APTC = Antiplatelet Trialists' Collaboration; C1 = cohort 1; EVEREST = Efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy; EXCITE = Efficacy and safety of ranibizumab in patients with Subfoveal Choroidal Neovascularization (CNV) secondary to age-related macular degeneration; EXTEND = Safety and efficacy of ranibizumab in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration; MARINA = Minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular AMD; PIER = Phase IIIb, multicenter, randomized, double-masked, sham injection–controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to AMD; SAILOR = Safety assessment of intravitreous lucentis for AMD; TIA = transient ischemic attack; Trt = treatment.

Table 3. Incidence of Systemic Events

Event	Study	Comparison Treatment 1 vs. Treatment 2	Treatment 1 n/N (%)	Treatment 2 n/N (%)	Treatment 1 Rate per 100 Patient-Years	Treatment 2 Rate per 100 Patient-Years
ATEs	MARINA[4]	Sham vs. ranibizumab 0.3 mg	13/236 (5.5)	17/238 (7.1)	3.14 (13/236/415)	3.85 (17/238/442)
		Sham vs. ranibizumab 0.5 mg	13/236 (5.5)	20/239 (8.4)	3.14 (13/236/415)	4.51 (20/239/444)
	ANCHOR[1,2]	Sham vs. ranibizumab 0.3 mg	11/143 (7.7)	7/137 (5.1)	4.73 (11/143/233)	2.76 (7/137/254)
		Sham vs. ranibizumab 0.5 mg	11/143 (7.7)	11/140 (7.9)	4.73 (11/143/233)	4.42 (11/140/249)
	PIER[16,17]	Sham vs. ranibizumab 0.3 mg	3/62 (4.8)	1/59 (1.7)	3.76 (3/62/80)	0.95 (1/59/105)
		Sham vs. ranibizumab 0.5 mg	3/62 (4.8)	2/61 (3.3)	3.76 (3/62/80)	0.95 (1/59/105)
	EVEREST[19]	Sham vs. ranibizumab 0.5 mg	0/21 (0.0)	0/40 (0.0)	0.00 (0/21/11)	0.00 (0/40/20)
	Overall	Sham vs. ranibizumab 0.3 mg	27/441 (6.1)	25/434 (5.8)	3.71 (27/441/727)	3.12 (25/434/801)
		Sham vs. ranibizumab 0.5 mg	27/462 (5.8)	33/480 (6.9)	3.66 (27/462/737)	4.04 (33/480/817)
MI	MARINA[4]	Sham vs. ranibizumab 0.3 mg	5/236 (2.1)	12/238 (5.0)	1.19 (5/236/420)	2.70 (12/238/444)
		Sham vs. ranibizumab 0.5 mg	5/236 (2.1)	6/239 (2.5)	1.19 (5/236/420)	1.33 (6/239/452)
	ANCHOR[1,2]	Sham vs. ranibizumab 0.3 mg	3/143 (2.1)	1/137 (0.7)	1.24 (3/143/241)	0.39 (1/137/257)
		Sham vs. ranibizumab 0.5 mg	3/143 (2.1)	6/140 (4.3)	1.24 (3/143/241)	2.36 (6/140/254)
	PIER[16,17]	Sham vs. ranibizumab 0.3 mg	1/62 (1.6)	1/59 (1.7)	1.22 (1/62/82)	0.95 (1/59/105)
		Sham vs. ranibizumab 0.5 mg	1/62 (1.6)	0/61 (0.0)	1.22 (1/62/82)	0.00 (0/61/107)
	EVEREST[19]	Sham vs. ranibizumab 0.5 mg	0/21 (0.0)	0/40 (0.0)	0.00 (0/21/11)	0.00 (0/40/20)
	Overall	Sham vs. ranibizumab 0.3 mg	9/441 (2.0)	14/434 (3.2)	1.21 (9/441/743)	1.74 (14/434/806)
		Sham vs. ranibizumab 0.5 mg	9/462 (1.9)	12/480 (2.5)	1.19 (9/462/754)	1.44 (12/480/833)
Stroke	MARINA[4]	Sham vs. ranibizumab 0.3 mg	3/236 (1.3)	3/238 (1.3)	0.71 (3/236/423)	0.66 (3/238/452)
		Sham vs. ranibizumab 0.5 mg	3/236 (1.3)	9/239 (3.8)	0.71 (3/236/423)	1.99 (9/239/453)
	ANCHOR[1,2]	Sham vs. ranibizumab 0.3 mg	3/143 (2.1)	3/137 (2.2)	1.25 (3/143/240)	1.17 (3/137/256)
		Sham vs. ranibizumab 0.5 mg	3/143 (2.1)	0/140 (0.0)	1.25 (3/143/240)	0.00 (0/140/260)
	PIER[16,17]	Sham vs. ranibizumab 0.3 mg	0/62 (0.0)	1/59 (1.7)	0.00 (0/62/83)	0.95 (1/59/105)
		Sham vs. ranibizumab 0.5 mg	0/62 (0.0)	0/61 (0.0)	0.00 (0/62/83)	0.00 (0/61/107)
	EVEREST[19]	Sham vs. ranibizumab 0.5 mg	0/21 (0.0)	0/40 (0.0)	0.00 (0/21/11)	0.00 (0/40/20)
	Overall	Sham vs. ranibizumab 0.3 mg	6/441 (1.4)	7/434 (1.6)	0.81 (6/441/745)	0.86 (7/434/813)
		Sham vs. ranibizumab 0.5 mg	6/462 (1.3)	9/480 (1.9)	0.79 (6/462/756)	1.07 (9/480/840)
Stroke + TIA	MARINA[4]	Sham vs. ranibizumab 0.3 mg	5/236 (2.1)	5/238 (2.1)	1.19 (5/236/421)	1.11 (5/238/451)
		Sham vs. ranibizumab 0.5 mg	5/236 (2.1)	12/239 (5.0)	1.19 (5/236/421)	2.67 (12/239/450)
	ANCHOR[1,2]	Sham vs. ranibizumab 0.3 mg	6/143 (4.2)	3/137 (2.2)	2.53 (6/143/237)	1.17 (3/137/256)
		Sham vs. ranibizumab 0.5 mg	6/143 (4.2)	4/140 (2.9)	2.53 (6/143/237)	1.56 (4/140/257)
	PIER[16,17]	Sham vs. ranibizumab 0.3 mg	1/62 (1.6)	1/59 (1.7)	1.22 (1/62/82)	0.95 (1/59/105)
		Sham vs. ranibizumab 0.5 mg	1/62 (1.6)	1/61 (1.6)	1.22 (1/62/82)	0.94 (1/61/106)
	EVEREST[19]	Sham vs. ranibizumab 0.5 mg	0/21 (0.0)	0/40 (0.0)	0.00 (0/21/11)	0.00 (0/40/20)
	Overall	Sham vs. ranibizumab 0.3 mg	12/441 (2.7)	9/434 (2.1)	1.62 (12/441/740)	1.11 (9/434/812)
		Sham vs. ranibizumab 0.5 mg	12/462 (2.6)	17/480 (3.5)	1.60 (12/462/751)	2.04 (17/480/833)
Vascular Death	MARINA[4]	Sham vs. ranibizumab 0.3 mg	3/236 (1.3)	2/238 (0.8)	0.71 (3/236/424)	0.44 (2/238/453)
		Sham vs. ranibizumab 0.5 mg	3/236 (1.3)	3/239 (1.3)	0.71 (3/236/424)	0.66 (3/239/457)
	ANCHOR[1,2]	Sham vs. ranibizumab 0.3 mg	3/143 (2.1)	1/137 (0.7)	1.23 (3/143/243)	0.39 (1/137/258)
		Sham vs. ranibizumab 0.5 mg	3/143 (2.1)	1/140 (0.7)	1.23 (3/143/243)	0.38 (1/140/260)
	PIER[16,17]	Sham vs. ranibizumab 0.3 mg	0/62 (0.0)	1/59 (1.7)	0.00 (0/62/83)	0.95 (1/59/105)
		Sham vs. ranibizumab 0.5 mg	0/62 (0.0)	0/61 (0.0)	0.00 (0/62/83)	0.00 (0/61/107)
	EVEREST[19]	Sham vs. ranibizumab 0.5 mg	0/21 (0.0)	0/40 (0.0)	0.00 (0/21/11)	0.00 (0/40/20)
	Overall	Sham vs. ranibizumab 0.3 mg	6/441 (1.4)	4/434 (0.9)	0.80 (6/441/750)	0.49 (4/434/816)
		Sham vs. ranibizumab 0.5 mg	6/462 (1.3)	4/480 (0.8)	0.79 (6/462/761)	0.47 (4/480/844)
APTC	MARINA[4]	Sham vs. ranibizumab 0.3 mg	10/236 (4.2)	16/238 (6.7)	2.39 (10/236/419)	3.61 (16/238/443)
		Sham vs. ranibizumab 0.5 mg	10/236 (4.2)	14/239 (5.9)	2.39 (10/236/419)	3.12 (14/239/449)
	ANCHOR[1,2]	Sham vs. ranibizumab 0.3 mg	8/143 (5.6)	5/137 (3.6)	3.37 (8/143/237)	1.96 (5/137/255)
		Sham vs. ranibizumab 0.5 mg	8/143 (5.6)	7/140 (5.0)	3.37 (8/143/237)	2.75 (7/140/254)
	PIER[16,17]	Sham vs. ranibizumab 0.3 mg	1/62 (1.6)	2/59 (3.4)	1.22 (1/62/82)	1.90 (2/59/105)
		Sham vs. ranibizumab 0.5 mg	1/62 (1.6)	0/61 (0.0)	1.22 (1/62/82)	0.00 (0/61/107)
	EVEREST[19]	Sham vs. ranibizumab 0.5 mg	0/21 (0.0)	0/40 (0.0)	0.00 (0/21/11)	0.00 (0/40/20)
	Overall	Sham vs. ranibizumab 0.3 mg	19/441 (4.3)	23/434 (5.3)	2.57 (19/441/738)	2.87 (23/434/803)
		Sham vs. ranibizumab 0.5 mg	19/462 (4.1)	21/480 (4.4)	2.54 (19/462/749)	2.53 (21/480/830)

APTC = Anti-Platelet Trialists Collaboration; ATE = arterial thromboembolic event; MI = myocardial infarction; TIA = transient ischemic attack.

comparison of ranibizumab 0.5 mg versus sham and ranibizumab 0.3 mg versus sham (Fig 1). Forest plots showing study-level results and pooled results (using the described modeling approaches) are summarized in Figure 2 for the 6 key endpoints. For comparisons of ranibizumab 0.5 mg or ranibizumab 0.3 mg with sham, 95% CIs all included 1, indicating no clinically meaningful treatment differences. Kaplan−Meier plots for these data over time are shown in Figure S3 (available at

Endpoint	Comparison Treatment 1 vs Treatment 2	Rate in Treatment 1 (n/N/PY)	Rate in Treatment 2 (n/N/PY)	Adjusted Hazard Ratio (95% CI)	P value[b]	More Common in Trt 1 | More Common in Trt 2
Death	Sham vs 0.3 mg	1.60 (12/441/750)	1.47 (12/434/816)	0.64 (0.30–1.39)	0.992	
	Sham vs 0.5 mg	1.58 (12/462/761)	1.07 (9/480/844)	0.80 (0.38–1.72)		
	0.3 mg vs 0.5 mg	1.59 (33/1764/2072)	1.94 (41/1814/2115)	1.25 (0.79–1.99)		
Hypertension	Sham vs 0.3 mg	13.19 (87/441/660)	9.77 (72/434/737)	0.79 (0.60–1.05)	0.781	
	Sham vs 0.5 mg	13.13 (88/462/670)	12.13 (91/480/750)	0.91 (0.69–1.20)		
	0.3 mg vs 0.5 mg	9.92 (191/1764/1925)	11.49 (224/1814/1950)	1.15 (0.95–1.39)		
Proteinuria	Sham vs 0.3 mg	0.13 (1/441/750)	0.00 (0/434/816)	Not Estimable	N/A	
	Sham vs 0.5 mg	0.13 (1/462/760)	0.00 (0/480/844)	Not Estimable		
	0.3 mg vs 0.5 mg	0.05 (1/1764/2071)	0.00 (0/1814/2115)	Not Estimable		
CHF	Sham vs 0.3 mg	2.87 (21/441/732)	2.75 (22/434/801)	0.91 (0.51–1.62)	0.908	
	Sham vs 0.5 mg	2.83 (21/462/743)	2.17 (18/480/829)	0.85 (0.48–1.51)		
	0.3 mg vs 0.5 mg	2.30 (47/1764/2044)	2.15 (45/1814/2090)	0.93 (0.62–1.41)		
Cardiac arrhythmia	Sham vs 0.3 mg	4.30 (31/441/720)	3.40 (27/434/794)	0.74 (0.46–1.18)	0.746	
	Sham vs 0.5 mg	4.24 (31/462/731)	3.80 (31/480/815)	0.92 (0.58–1.46)		
	0.3 mg vs 0.5 mg	3.40 (69/1764/2031)	4.08 (84/1814/2061)	1.24 (0.90–1.71)		
Acute renal failure	Sham vs 0.3 mg	1.21 (9/441/745)	1.36 (11/434/807)	0.82 (0.35–1.94)	0.898	
	Sham vs 0.5 mg	1.19 (9/462/755)	0.95 (8/480/838)	1.00 (0.44–2.31)		
	0.3 mg vs 0.5 mg	1.07 (22/1764/2059)	1.33 (28/1814/2104)	1.22 (0.70–2.14)		
GI hemorrhage/ perforation	Sham vs 0.3 mg	1.08 (8/441/744)	1.74 (14/434/804)	1.57 (0.69–3.60)	0.996	
	Sham vs 0.5 mg	1.06 (8/462/754)	1.81 (15/480/830)	1.79 (0.78–4.07)		
	0.3 mg vs 0.5 mg	1.36 (28/1764/2054)	1.48 (31/1814/2095)	1.14 (0.68–1.90)		
VTE	Sham vs 0.3 mg	0.53 (4/441/748)	0.74 (6/434/811)	1.14 (0.32–4.10)	0.969	
	Sham vs 0.5 mg	0.53 (4/462/758)	0.12 (1/480/842)	0.60 (0.15–2.33)		
	0.3 mg vs 0.5 mg	0.68 (14/1764/2064)	0.38 (8/1814/2112)	0.53 (0.22–1.27)		
Wound healing	Sham vs 0.3 mg	0.80 (6/441/746)	0.74 (6/434/813)	1.02 (0.36–2.89)	0.993	
	Sham vs 0.5 mg	0.79 (6/462/756)	0.84 (7/480/836)	1.04 (0.37–2.92)		
	0.3 mg vs 0.5 mg	0.78 (16/1764/2063)	0.81 (17/1814/2104)	1.02 (0.51–2.02)		

Hazard Ratio (95% CI): 0.01   0.1   1   10

Figure 4. Pairwise comparisons of other systemic events in ranibizumab 0.5 mg, ranibizumab 0.3 mg, and sham.[a] Horizontal bars are 95% confidence intervals (CIs) of the hazard ratio (HR), reported as Trt 2 vs Trt 1. [a]Cox regression, stratified by study. [b]Interaction test for homogeneity from global Cox regression model adjusting for baseline risk factors. Numbers in the table are rates per 100 patient-years (Rate) and the number of subjects with the event (n)/ number of subjects (N)/number of patient-years (PY). CHF = congestive heart failure; GI = gastrointestinal; Trt = treatment; VTE = venous thromboembolism.

www.ophthalmologyretina.org). Event proportions and incidence rates for these systemic endpoints per 100 patient-years are shown for primary comparisons in Table 3.

When comparing ranibizumab 0.5 mg and 0.3 mg doses, the rates of MI, stroke (excluding TIA), vascular death, and APTC events were similar between dose groups (Fig 1). Adjusted HR CIs for the comparisons between ranibizumab 0.5 mg versus ranibizumab 0.3 mg did exclude 1 for the stroke or TIA endpoint (HR, 1.85; 95% CI, 1.13–3.05) and overall ATEs (HR, 1.41; 95% CI, 1.02–1.95). Results from the global and pairwise models were similar for all endpoints evaluated.

Other Systemic Events

Other systemic endpoints including all-cause death, hypertension, proteinuria, congestive heart failure, cardiac arrhythmia, acute renal failure, gastrointestinal hemorrhage or perforation, venous thromboembolism, and wound healing were similar between ranibizumab 0.5 mg or 0.3 mg and sham treatment and between ranibizumab 0.5 mg and 0.3 mg (Fig 4).

Discussion

This pooled analysis evaluates patient-level data from 7 pooled Genentech and Novartis phase II, III, and IV studies comprising 4080 patients with nAMD, including 1764 and 1854 patients treated with ranibizumab 0.3 and 0.5 mg, respectively.

Rates of ATE events including MI, stroke (excluding TIA), stroke or TIA, vascular death, and APTC events were low over the 1- to 2-year evaluation periods, and there were no clinically or statistically meaningful treatment differences observed between ranibizumab 0.5 mg or 0.3 mg versus sham. None of the measures of MI, stroke, stroke or TIA, vascular death, or the composites APTC or ATE showed a significant or clinically meaningful difference in this pooled analysis when comparing ranibizumab 0.5 mg or 0.3 mg versus sham. These data do not suggest an increased risk of vascular AEs with ranibizumab 0.5 mg or 0.3 mg compared with sham in patients with nAMD.

These findings are consistent with previous meta-analyses of interventional clinical trials in patients with nAMD, which generally have not demonstrated an increased risk of CVAs, major cardiovascular events, ATEs, or mortality of ranibizumab compared with sham treatment.[26-28] In practice, claims data from the 7 health administrative databases of Ontario showed no significant increase in risk of stroke, acute MI, venous thromboembolism, or congestive heart failure in patients treated with ranibizumab.[29] Real-world data from the Centers for

Medicare and Medicaid Services showed that patients with AMD treated with ranibizumab had a significantly lower risk of MI or mortality than patients treated with verteporfin.[10,11,30]

The randomized clinical trials used in this analysis were designed to demonstrate the efficacy of the therapeutic agents involved. Statistically, to demonstrate visual or anatomic improvement over sham, the trials were sufficiently powered because of robust differences in efficacy. After the demonstration of efficacy of ranibizumab based on the sham-controlled randomized clinical trials, it is no longer ethical to conduct further sham-controlled trials, limiting the number of patients available for comparisons of ranibizumab versus sham in a pooled analysis. Another limitation is created by low event rates (e.g., for stroke without TIA, for which an upper limit of 3.77 for the HR was obtained). The incidence rates per 100 patient-years were 0.8 (sham) and 1.1 (ranibizumab 0.5 mg). Approximately 1000 patients per group would be required to obtain an upper confidence limit below 3. With no new sham-controlled trials being conducted, it will not be possible to obtain such large numbers of randomized sham-controlled trials for analysis.

Strengths of the Pooled Analysis

Pooling patient-level data from these 7 combined studies provides increased precision in estimating treatment differences and allows for an adjustment for baseline characteristics and for pooling results across studies of differing durations.[31] Availability of the timing of each AE allowed for Kaplan−Meier plots (Fig S3, available at www.ophthalmologyretina.org) and fitting of Cox Regression models. The Kaplan−Meier plots show event rates over time incorporating the differing study durations. The "global model" adjusted for relevant baseline risk factors. All fitted models were stratified by study (adjusting for study differences), and global model results were consistently similar to those of the pairwise comparisons, indicating that adjustment for potential baseline risk factors had little influence on the outcome.

This pooled analysis followed a prospective, prespecified plan for the pooling of heterogeneous studies, definition of endpoints, and analysis methods. To our knowledge, this is the largest collaborative database of ranibizumab clinical safety events in patients with nAMD, including Genentech and Novartis phase II, III, and IV clinical trials.

Limitations of the Pooled Analysis

An inherent limitation of pooled analyses is the pooling of heterogeneous studies, which differ in study design, inclusion and exclusion criteria, treatment duration, dosing regimen, PRN re-treatment criteria, patient population, and region). This analysis combined trials with monthly treatment (MARINA, ANCHOR, EXTEND I), PRN treatment (EVEREST, SAILOR), and quarterly treatment (PIER, EXCITE). The primary comparison of ranibizumab 0.5 mg with sham included mostly monthly-treated patients (82% of primary comparison population). These analyses were limited in the extent to which they could evaluate exposure

to ranibizumab or different dosing regimens. Because the number of events was low in each group, it was not practical or meaningful to stratify by treatment regimen.

This analysis did not adjust for multiplicity, which could increase the probability of chance findings. For the primary comparisons, the 95% CIs did intersect 1, so an adjustment for multiplicity would only widen the CIs.

Many of the events examined in this analysis resulted in discontinuation of the patient from the study. As such, data are not typically collected for a patient after treatment discontinuation. Therefore, for the most part, data on multiple occurrences of the safety events presented here are not available.

Meta-analyses, even with increased numbers of patients, also may be underpowered to evaluate treatment differences in uncommon safety events.[27] A prospectively designed study with patient numbers similar to this pooled analysis would be underpowered to detect differences for AEs that occur infrequently for comparisons with sham (e.g., to detect 1% vs. 2%, 16% power; 1% vs. 3%, 52% power; 4% vs. 8%, 70% power; 4% vs. 12%, 99% power). Thus, for stroke, assuming a 1% rate in the sham group, there is only 52% power to detect a tripling of the risk, whereas for APTC events assuming a 4% rate in the sham group, there is 70% power to detect a doubling of the rate. Composite endpoints may increase power to detect treatment differences but can mask or dilute the influence that any particular component may have shown in isolation.

In the included clinical trials, risk factors for systemic vascular events were not collected in a standardized way as for cardiovascular safety studies (e.g., central event adjudication incorporated for the ascertainment and verification of clinical safety events). The strict inclusion and exclusion criteria and required visits of clinical trials usually result in patients who are healthier and more closely followed than those who receive medical care in clinical practice, and these patients often receive better care during the clinical trials. This may limit extrapolation of pooled analysis results to the wider study population. In ANCHOR, MARINA, and PIER, there were no exclusion criteria related to cardiovascular, cerebrovascular, or peripheral vascular conditions. SAILOR excluded patients with uncontrolled cardiovascular disease, and EVEREST, EXTEND I, and EXCITE excluded patients with prior CVA; however, these studies provided a small part of the study population for the pertinent comparisons (EVEREST: 6% for the sham vs. 0.5 mg comparison; EXTEND I, EXCITE: 8% for the 0.3 mg vs. 0.5 mg comparison).

Conclusions

This patient-level, data-pooled analysis draws together the body of company-sponsored trials, allowing for an increased sensitivity in detecting infrequent AEs. Within its limitations, this analysis confirmed the low rates of cardiovascular and cerebrovascular events in patients with nAMD treated with intravitreal ranibizumab 0.5 mg or 0.3 mg, and these low rates did not appear to be clinically or statistically significantly different from sham treatment. This analysis

adds to the substantial postmarketing experience, and the results are consistent with the established safety of ranibizumab in patients with nAMD. Taken together, the results from this pooled analysis support the established benefit–risk profile of ranibizumab in patients with nAMD.

The extrapolation of the findings of this analysis to the real-world population is limited by the enrollment criteria of the selected studies, because the patients in clinical studies may be healthier and treated more attentively than their counterparts in the wider population. Although it would not be ethical to have sham-controlled nAMD studies in the future because of the significant benefit of anti-VEGF therapy, ongoing safety analyses of real-world data such as healthcare claims analyses, hospital record analyses, and observational studies such as LUMINOUS[32] should be continued to further investigate the systemic safety of ranibizumab in clinical practice.

References

1. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355:1432–1444.
2. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology.* 2009;116:57–65.e55.
3. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology.* 2014;121:2181–2192.
4. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355:1419–1431.
5. Xu L, Lu T, Tuomi L, et al. Pharmacokinetics of ranibizumab in patients with neovascular age-related macular degeneration: a population approach. *Invest Ophthalmol Vis Sci.* 2013;54:1616–1624.
6. Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. *Nat Rev Clin Oncol.* 2009;6:465–477.
7. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2011;364:1897–1908.
8. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology.* 2006;113:363–372.e365.
9. *Eylea (aflibercept) injection prescribing information.* Tarrytown, NY: Regeneron Pharmaeutics, Inc; 2015. Available at: https://www.regeneron.com/Eylea/eylea-fpi.pdf. Accessed May 4, 2016.
10. Fernandez AB, Wong TY, Klein R, et al. Age-related macular degeneration and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *Ophthalmology.* 2012;119:765–770.
11. Thomas J, Mohammad S, Charnigo R, et al. Age-related macular degeneration and coronary artery disease in a VA population. *South Med J.* 2015;108:502–506.
12. Hu CC, Ho JD, Lin HC. Neovascular age-related macular degeneration and the risk of stroke: a 5-year population-based follow-up study. *Stroke.* 2010;41:613–617.
13. Ikram MK, Mitchell P, Klein R, et al. Age-related macular degeneration and long-term risk of stroke subtypes. *Stroke.* 2012;43:1681–1683.
14. Wieberdink RG, Ho L, Ikram MK, et al. Age-related macular degeneration and the risk of stroke: the Rotterdam study. *Stroke.* 2011;42:2138–2142.
15. Tan JS, Wang JJ, Liew G, et al. Age-related macular degeneration and mortality from cardiovascular disease or stroke. *Br J Ophthalmol.* 2008;92:509–512.
16. Abraham P, Yue H, Wilson L. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. *Am J Ophthalmol.* 2010;150:315–324.e311.
17. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol.* 2008;145:239–248.
18. 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;116:1731–1739.
19. Koh A, Lee WK, Chen LJ, et al. EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina.* 2012;32:1453–1464.
20. Tano Y, Ohji M. EXTEND-I: safety and efficacy of ranibizumab in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Acta Ophthalmol.* 2010;88:309–316.
21. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology.* 2011;118:831–839.
22. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology.* 2013;120:1046–1056.
23. Zarbin MA, Dunger-Baldauf C, Haskova Z, et al. Vascular safety of ranibizumab in patients with diabetic macular edema: a pooled analysis of patient-level data from randomized clinical trials. *JAMA Ophthalmol.* 2017;135:424–431.
24. *Lucentis (ranibizumab injection) intravitreal injection prescribing information.* South San Francisco, CA: Genentech, Inc; 2015. Available at: http://www.gene.com/download/pdf/lucentis_prescribing.pdf. Accessed May 4, 2016.
25. *Lucentis (ranibizumab) summary of product characteristics.* Basel, Switzerland: Novartis Pharma; 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000715/WC500043546.pdf. Accessed May 4, 2016.
26. Bressler NM, Boyer DS, Williams DF, et al. Cerebrovascular accidents in patients treated for choroidal neovascularization

with ranibizumab in randomized controlled trials. *Retina*. 2012;32:1821–1828.

27. Thulliez M, Angoulvant D, Le Lez ML, et al. Cardiovascular events and bleeding risk associated with intravitreal anti-vascular endothelial growth factor monoclonal antibodies: systematic review and meta-analysis. *JAMA Ophthalmol*. 2014;132:1317–1326.

28. Ueta T, Noda Y, Toyama T, et al. Systemic vascular safety of ranibizumab for age-related macular degeneration: systematic review and meta-analysis of randomized trials. *Ophthalmology*. 2014;121:2193–2203.e2191-2197.

29. Campbell RJ, Gill SS, Bronskill SE, et al. Adverse events with intravitreal injection of vascular endothelial growth

factor inhibitors: nested case-control study. *BMJ*. 2012;345: e4203.

30. Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol*. 2010;128:1273–1279.

31. Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Eval Health Prof*. 2002;25:76–97.

32. Holz FG, Bandello F, Gillies M, et al. Safety of ranibizumab in routine clinical practice: 1-year retrospective pooled analysis of four European neovascular AMD registries within the LUMI-NOUS programme. *Br J Ophthalmol*. 2013;97:1161–1167.

Footnotes and Financial Disclosures

[1] Institute of Ophthalmology and Visual Science, Rutgers-New Jersey Medical School, Rutgers University, Newark, New Jersey.

[2] Genentech, Inc, South San Francisco, California.

[3] Novartis Pharma, Basel, Switzerland.

[4] Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, Nova Scotia, Canada.

[5] Department of Biomedical and Clinical Science "Luigi Sacco," Sacco Hospital, University of Milan, Milan, Italy.

Abbreviations and Acronyms:

AE = adverse event; **AMD** = age-related macular degeneration; **APTC** = Antiplatelet Trialists' Collaboration; **ATE** = arterial thromboembolic event; **CI** = confidence interval; **CVA** = cardiovascular accident; **HR** = hazard ratio; **MI** = myocardial infarction; **nAMD** = neovascular age-related macular degeneration; **PRN** = pro re nata; **SMQs** = Standardized Medical Dictionary for Regulatory Activities queries; **TIA** = transient ischemic attack; **VEGF** = vascular endothelial growth factor.

Correspondence:

Marco A. Zarbin, MD, PhD, Institute of Ophthalmology and Visual Science, Rutgers-New Jersey Medical School, Rutgers University, Doctors Office Center, Suite 6100, 90 Bergen St, Newark, NJ 07103. E-mail: zarbin@earthlink.net.