


Original Investigation

Cardiovascular Events and Bleeding Risk Associated With Intravitreal Antivascular Endothelial Growth Factor Monoclonal Antibodies

Systematic Review and Meta-analysis

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IMPORTANCE Few data exist regarding the systemic safety of intravitreal antivascular endothelial growth factor (anti-VEGF) monoclonal antibody (mAb).

OBJECTIVE To conduct a systematic review and meta-analysis to evaluate the risk of major cardiovascular and nonocular hemorrhagic events in patients with neovascular age-related macular degeneration (AMD), diabetes mellitus-associated macular edema (DME), or retinal vein occlusions (RVOs) who receive intravitreal anti-VEGF mAbs.

DATA SOURCES The MEDLINE and Cochrane Central databases were searched for potentially eligible studies.

STUDY SELECTION Randomized clinical trials comparing ranibizumab or bevacizumab with no anti-VEGF treatment, as well as those comparing ranibizumab with bevacizumab in patients with AMD, DME, or RVOs.

DATA EXTRACTION AND SYNTHESIS We used a fixed-effects model and report the results as odds ratios (ORs) and 95% CIs.

MAIN OUTCOMES AND MEASURES Primary end points were major cardiovascular and nonocular hemorrhagic events. Secondary end points were all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, venous thromboembolic events (VTEs), and hypertension.

RESULTS Twenty-one trials that evaluated 9557 patients were retrieved. Anti-VEGF mAbs did not significantly increase the risk of major cardiovascular events (OR, 1.18; 95% CI, 0.81-1.71) or nonocular hemorrhagic events (OR, 1.42; 95% CI, 0.95-2.13) in treatment groups compared with control populations. Bevacizumab did not increase the risk of major cardiovascular events (OR, 0.94; 95% CI, 0.59-1.52) or nonocular hemorrhagic events (OR, 2.56; 95% CI, 0.78-8.38) compared with ranibizumab, but significantly increased VTEs (OR, 3.45; 95% CI, 1.25-9.54). Subgroup analysis showed a significant increase of nonocular hemorrhagic events in patients with AMD in ranibizumab vs control trials (OR, 1.57; 95% CI, 1.01-2.44). Anti-VEGF mAbs did not significantly increase overall mortality, cardiovascular mortality, stroke, myocardial infarction, VTEs, or hypertension.

CONCLUSIONS AND RELEVANCE We showed that intravitreal anti-VEGF-mAbs were not associated with significant increases in major cardiovascular or nonocular hemorrhagic events, but studies and meta-analyses were not powered enough to correctly assess these risks. Increased risks of VTEs with bevacizumab and nonocular hemorrhagic events in older patients with AMD with ranibizumab should be cautiously interpreted because more safety data are needed.

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Neovascular age-related macular degeneration (AMD) is the leading cause of vision loss among elderly people in developed countries.¹⁻³ Diabetes mellitus-associated macular edema (DME) is the main cause of vision loss in the working age population, followed by retinal vein occlusion (RVO).⁴ Treatment of these diseases is of major importance in delaying vision loss in this elderly patient population, and therefore in providing functional benefit. Treatment options for neovascular AMD include laser photocoagulation and verteporfin photodynamic therapy; treatment options for DME and RVO include laser photocoagulation and intravitreal injection of corticosteroids.

The vascular endothelial growth factor (VEGF)-A isoform is a cytokine that promotes angiogenesis and vascular permeability.⁵ Expression of VEGF is upregulated in pathologic conditions such as hypoxia in regions of the ischemic retina⁶⁻⁸ or hyperglycemia.⁹ Several anti-VEGF treatments are available for treatment of macular edema: pegaptanib sodium, aflibercept, and 2 monoclonal antibodies (mAbs): ranibizumab and bevacizumab. Ranibizumab, a humanized mAb fragment, is the only approved mAb for treatment of AMD, DME, and RVO in Europe and the United States.¹⁰ Bevacizumab, a full-length humanized antibody, is approved for the treatment of metastatic solid cancers¹¹ but is widely used as an off-label treatment for AMD, DME, and RVO. Its off-label use is worthwhile because of its lower cost compared with other treatments¹² and comparable efficacy.¹³ Anti-VEGF agents administered by intravitreal injection block the action of VEGF-A isoforms, inhibit VEGF-driven neovascularization,¹⁴ and have shown efficacy in preserving visual acuity in AMD,¹⁵ DME,¹⁶ and RVO.^{17,18}

However, the systemic safety of these intravitreal agents is unknown. Systemic use of bevacizumab in colorectal cancer therapy has been associated with serious cardiovascular adverse effects, such as hypertension,¹⁹ arterial thromboembolic events,²⁰ hemorrhage,²¹ and death.²² Because intravitreal antiangiogenic agents have been associated with detectable levels in the systemic circulation,^{23,24} there is a rationale for the potential occurrence of systemic adverse events. Although intravitreal bevacizumab is administered at a dose of 1.0 to 2.5 mg (150 times less than the systemic dose used in cancer),²⁵ VEGF inhibition may induce systemic adverse effects that could be serious for patients with diabetes or elderly patients who are at increased risk for cardiovascular adverse events.²⁶ Moreover, some clinical trials²⁷ suggested that intravitreal use of ranibizumab was associated with a small increase in nonocular hemorrhage risk.

To address these issues, we performed a systematic review and meta-analysis of clinical trials to investigate the risk of cardiovascular adverse events and nonocular hemorrhage associated with intravitreal use of the anti-VEGF mAbs ranibizumab and bevacizumab in patients with wet AMD, DME, and RVO.

Methods

Information Sources and Search Strategy

Studies were identified by searching MEDLINE and Cochrane Central Register of Controlled Trials databases from inception until June 30, 2013, without language restrictions. The following key words were used: *bevacizumab*, *ranibizumab*, *intravitreal*, *clinical trial*, and *randomized controlled trial*. We also reviewed the reference lists of meta-analyses and selected studies (eTable 1 in the Supplement).

Eligibility Criteria and Study Selection

The selection of eligible studies was done by one author (M.T.). Inclusion criteria were parallel randomized clinical trials comparing intravitreal ranibizumab or bevacizumab with no treatment (sham) or a non-antiangiogenic treatment in patients with wet AMD, DME, or RVO. Trials that compared different treatment regimens of ranibizumab or bevacizumab were also included in this systematic review for a dose-response analysis. To address clinically relevant cardiovascular outcomes as well as mortality, we only included studies with a minimum 3-month follow-up period.

Risk of Bias Assessment

Two authors (M.T. and T.B.-A.) assessed the methodologic quality of the selected trials according to the Cochrane risk of bias criteria. We considered the following domains: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) masking of participants and personnel (performance bias), and (4) masking of outcome assessment (detection bias) for adverse events. We considered the risk of bias to be low if masking of participants, personnel, and outcome assessment was adequate; otherwise, the risk of bias was considered to be unknown or high.

End Points

Our main end points were major cardiovascular events using the Antiplatelet Trialists' Collaboration (APTC) criteria²⁸ and nonocular hemorrhage events. The APTC end point is a composite of nonfatal myocardial infarction, nonfatal ischemic or hemorrhagic stroke, or death due to a vascular or unknown cause. Secondary end points included all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, venous thromboembolic events (VTEs), arterial hypertension, and proteinuria.

Data Extraction

End point data from eligible trials were extracted by one author (M.T.), with a full review of the data extracted by a second author (T.B.-A.), and differences were adjudicated by both authors. We extracted data from the longest follow-up period whenever possible and if fewer than 10% of patients crossed over from the control to active treatment group. When crossover was above 10% we included only data collected before the crossover.

Statistical Analysis

We extracted aggregate data from published reports. We report the results as odds ratios (ORs) with 95% CIs. We conducted a fixed-effects meta-analysis using the Peto method²⁹ because it is more powerful and less biased in cases of low event rates and no significant imbalance between treatment groups.

Our main comparison was anti-VEGF treatment vs control. In trials that evaluated 2 or more doses of the same mAb we preserved randomization but collapsed the different dose intervention arms (eg, ranibizumab, 0.3 mg and 0.5 mg) into single treatment arms. Secondary comparisons were bevacizumab vs ranibizumab and high-dose vs low-dose regimens. This latter comparison was possible only for studies that evaluated 2 or more doses of the same mAb (ranibizumab-only studies).

Statistical heterogeneity across trials was assessed with χ^2 and I^2 tests. Heterogeneity was considered significant if the P value was $<.1$ and considered high if the I^2 value was above 50%. We planned subgroup analysis to investigate the effect of different covariates on outcome measures: the type of mAb used (ranibizumab or bevacizumab), type of disease (AMD, DME, or RVO), follow-up duration, and study quality.

For primary outcomes, we conducted sensitivity analysis using the fixed Mantel-Haenszel method with a classical (0.5) and a treatment arm continuity correction as described by Sweeting et al³⁰ and with a logistic method. We performed sensitivity analyses to evaluate the impact of studies in which the control treatment was known to be associated with adverse cardiovascular events (eg, verteporfin).

Publication bias was assessed by examination of the funnel plot asymmetry. The rank correlation test and the weighted linear regression test were used to test for funnel plot asymmetry. Statistical analyses were performed using Revman, version 5.1, and R software, version 2.11.1³¹ (the meta package³²).

Results

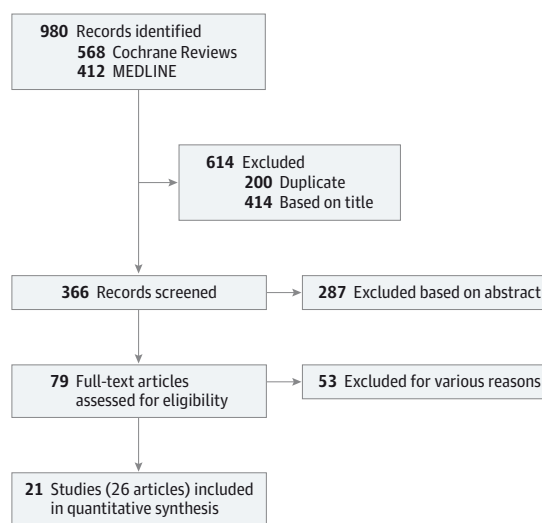
Included Studies

The number of studies identified at each stage of the systematic review is shown in **Figure 1**. After removing duplicate references, the searches identified 780 records. According to our selection criteria, 21 randomized clinical trials^{13,17,18,27,33-54} were retrieved including 9557 patients (**Table**).

Twelve studies^{13,27,33-46} included patients with AMD (6616 patients; mean age, 78 years) and compared ranibizumab vs control (4 studies), 2 doses of ranibizumab (3 studies), bevacizumab vs control (1 study), and ranibizumab vs bevacizumab (4 studies).

Seven studies⁴⁷⁻⁵² included patients with DME (2152 patients; mean age, 63 years) and compared ranibizumab vs control (6 studies) or bevacizumab vs control (1 study). Two studies^{55,56} were excluded because 2 eyes per patient were possibly randomized and data for adverse events were reported by studied eye rather than by patient. We decided to retain data from the Elman et al⁵⁰ study, even if 2 eyes were possibly randomized, because the authors reported adverse events data by

Figure 1. Flow Diagram of Study Selection



The main reasons for exclusion of full-text articles were absence of adverse events reporting or absence of details regarding adverse events.

participants. Two studies^{17,18,53,54} included patients with RVO (n = 789) and evaluated ranibizumab vs sham injections.

Comparison between ranibizumab and control treatment included 12 studies (n = 4346),* between bevacizumab and control included 2 studies (n = 332),^{42,52} and between bevacizumab and ranibizumab included 4 studies (n = 2181).^{13,43-46} Follow-up for adverse events was 24 months in 5 studies, 12 months in 13 studies, and less than 12 months in 3 studies. Ten studies compared a high dose with a low dose of ranibizumab: either 0.5 mg or 0.3 mg on a monthly basis, or the same dose in a monthly vs quarterly regimen. For this comparison longer follow-up was possible.

Risk of Bias

Twelve studies (57%) were considered to be at low risk regarding consideration of both performance and detection bias (**Table**, **Figure 2**, and eFigure 1 in the Supplement). Selection bias was judged at low risk in 13 studies (62%) and unknown (information missing) in 8 studies (38%).

Major Cardiovascular Events

Anti-VEGF mAb treatment did not significantly increase the risk of major cardiovascular events (APTC criteria) compared with control treatment, with no significant heterogeneity (OR, 1.18; 95% CI, 0.81-1.71; $P = .38$; $I^2 = 0\%$) (**Figure 3** and eTable 2 in the Supplement). No asymmetry was observed in the funnel plot (eFigure 2 in the Supplement). The results did not change in sensitivity analysis when different methods to pool the data were used (eTable 3 in the Supplement) or when trials with active verteporfin treatment were excluded (OR, 1.12; 95% CI, 0.76-1.67; $P = .56$). We found no significant effect of follow-up duration in ranibizumab studies ($P = .97$ for interaction) (eTable 4 in the Supplement). The type of disease, type

*References 17, 18, 27, 33-38, 47-51, 53, 54

Table. Characteristics of Included Studies

Source	Disease/Design/ Follow-up	No. of Patients/Eyes (% Women)	Mean Age (Range), y	Active/ Control Treatment	Exclusion if CVD History	Efficacy Outcome	Safety Outcome ^a	Risk of Bias
MARINA, ²⁷ 2006 ^b	AMD/ double-masked/ 24 mo	716/716 (65)	77 (52-95)	Ranibizumab/ sham	No	Proportion of patients losing <15 letters at 12 mo (primary end point)	Succinct report of AEs; incidence and severity of ocular and nonocular AEs	Low
ANCHOR, ^{33,34} 2006, 2009	AMD/ double-masked/ 12 mo ^c	423/423 (50)	77 (53-97)	Ranibizumab/ verteporfin	No	Patients losing <15 letters from baseline VA at 12 mo (primary end point)	Succinct report of AEs; incidence and severity of ocular and nonocular AEs	Low
FOCUS, ^{35,36} 2006, 2008	AMD/ single-masked/ 24 mo	162/162 (53)	74 (50-93)	Ranibizumab plus verteporfin/sham	Unclear	Proportion of patients losing <15 letters at 12 mo (primary end point)	Succinct report of AEs; incidence and severity of ocular and nonocular AEs at 24 mo (primary end point)	Unclear or high
PIER, ^{37,38} 2008, 2010 ^b	AMD/ double-masked/ 12 mo ^c	184/184 (60)	78 (54-94)	Ranibizumab/ sham	Unclear	Mean change from baseline to 12 mo in VA score (primary end point); crossover after 12 mo	Succinct report of AEs; incidence and severity of ocular and nonocular AEs	Low
SAILOR, ³⁹ 2009 ^b	AMD/ single-masked/ 12 mo	2378/2378 (59)	79 (51-101)	Ranibizumab/ ranibizumab	No	Several efficacy end points including changes in BCVA over time	Succinct report of AEs; incidence of ocular and nonocular serious AEs evaluated through 12 mo (primary end point, but no formal hypothesis testing)	Unclear or high
EXTEND-I, ⁴⁰ 2010 ^b	AMD/ open-label/ 12 mo	88/88 (23)	70 (NR)	Ranibizumab/ ranibizumab	Unclear	Mean change from baseline in BCVA score at 6 mo (primary end point)	Succinct report of AEs; incidence of grade 3 targeted AE in study eye and fellow eye up to 6 mo (primary end point)	Unclear or high
EXCITE, ⁴¹ 2011 ^b	AMD/ double-masked/ 12 mo	353/353 (59)	75 (50-83)	Ranibizumab/ ranibizumab	Unclear	Mean change in BCVA at 12 mo (primary end point)	Succinct report of AEs, serious AEs, and changes in vital signs assessed monthly	Unclear or high
ABC, ⁴² 2010	AMD/ double-masked/ 12 mo	131/131 (47)	80 (50-85)	Bevacizumab/ verteporfin, sham	Yes	Proportion of patients gaining ≥15 letters of VA at 1 y (primary end point)	ATEs specifically assessed: AE report at each visit	Low
Subramanian et al, ⁴³ 2010	AMD/ double-masked/ 12 mo	28/28 (4)	79 (NR)	Ranibizumab/ bevacizumab	Yes	VA and foveal thickness at 1 y (primary outcomes); 135 patients initially planned	ATEs specifically assessed; ocular and systemic AEs (eg, BP, gastrointestinal, thromboembolic disease)	Low
CATT, ^{13,44} 2011, 2012	AMD/ single-masked/ 24 mo	1208/1208 (61)	79 (50-90)	Ranibizumab/ bevacizumab	No	Mean change in VA between baseline and 1 y (primary outcome)	Succinct report of AEs; incidence of ocular and systemic AEs	Unclear or high
IVAN, ⁴⁵ 2012	AMD/ double-masked/ 12 mo	628/628 (60)	78 (NR)	Ranibizumab/ bevacizumab	No	BCVA measured as ETDRS at 2 y (primary outcome, study ongoing)	ATEs specifically assessed; occurrence of an arteriothrombotic event or heart failure	Low
MANTA, ⁴⁶ 2013	AMD/ double-masked/ 12 mo	317/317 (64)	77 (NR)	Ranibizumab/ bevacizumab	Yes	Mean change in BCVA between baseline and 1 y (primary outcome); 4 and 2 patients received the same drug in the fellow eye during follow-up	Succinct report of AEs	Low
READ-2, ⁴⁷ 2009 ^d	DME/ open-label/ 6 mo	126/126 (58)	62 (NR)	Ranibizumab/ laser	Unclear	Change from baseline in BCVA at 6 mo (primary outcome)	Succinct report of safety evaluations	Unclear or high
RESOLVE, ⁴⁸ 2010	DME/ double-masked/ 12 mo	151/151 (46)	64 (32-85)	Ranibizumab/ sham	Unclear	Mean change in BCVA from baseline to 1 mo through 12 mo	Succinct report of serious AEs	Unclear or high
RESTORE, ⁴⁹ 2011	DME/ double-masked/ 12 mo	345/345 (42)	63 (54-72)	Ranibizumab plus laser/sham	Yes	Mean change in BCVA from baseline to 1 mo through 12 mo and safety (primary outcome)	Succinct report of incidence of AEs and serious AEs at 12 mo	Low

(continued)

Table. Characteristics of Included Studies (continued)

Source	Disease/Design/ Follow-up	No. of Patients/Eyes (% Women)	Mean Age (Range), y	Active/ Control Treatment	Exclusion if CVD History	Efficacy Outcome	Safety Outcome ^a	Risk of Bias
Elman et al, ⁵⁰ 2010 ^e	DME/ single-masked/ 12 mo	691/854 (44)	63 (55-70)	Ranibizumab/ sham, triamcinolone	Yes	Mean change in VA at 1 y, adjusted for baseline VA (primary outcome)	Succinct report of safety (could be assessed at patient level, and participants with 2 study eyes were assigned to the non- sham group)	Unclear or high
RIDE, ⁵¹ 2012 ^b	DME/ double-masked/ 24 mo	382/382 (43)	63 (53-74)	Ranibizumab/ sham	Yes	Proportion of patients gaining 15 ETDRS letters in BCVA score at 24 mo (primary outcome)	Succinct evaluations included vital signs, safety assessments	Low
RISE, ⁵¹ 2012 ^b	DME/ double-masked/ 24 mo	377/377 (44)	62 (52-72)	Ranibizumab/ sham	Yes	Proportion of patients gaining 15 ETDRS letters in BCVA score at 24 mo (primary outcome)	Succinct evaluations included vital signs, safety assessments	Low
BOLT, ⁵² 2010	DME/ open-label/ 12 mo	80/80 (31)	64 (40-86)	Bevacizumab/ laser	Yes	Mean difference in ETDRS BCVA at 12 mo	ATEs specifically assessed; systemic AEs, including thromboembolic events, BP, and ECG findings, at 12 mo	Unclear or high
BRAVO, ^{17,53} 2010, 2011 ^{b,f}	RVO/ double-masked/ 6 mo	397/397 (47)	66 (26-91)	Ranibizumab/ sham	Yes	Mean change from baseline BCVA letter score at 6 mo (primary outcome)	Succinct report of incidence and severity of ocular and nonocular AEs and serious AEs	Low
CRUISE, ^{18,54} 2010, 2011 ^{b,f}	RVO/ double-masked/ 6 mo	392/392 (43)	68 (20-91)	Ranibizumab/ sham	Yes	Mean change from baseline BCVA letter score at 6 mo (primary outcome)	Succinct report of incidence and severity of ocular and nonocular AEs and serious AEs	Low

Abbreviations: ABC, Avastin (Bevacizumab) for Choroidal Neovascular Age Related Macular Degeneration; AE, adverse event; AMD, age-related macular degeneration; ANCHOR, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; ATEs, atherothrombotic events; BCVA, best-corrected visual acuity; BOLT, Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema; BP, blood pressure; BRAVO, Ranibizumab for the Treatment of Macular Edema Following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; CATT, Comparison of Age-Related Macular Degeneration Treatments Trials; CRUISE, Ranibizumab for the Treatment of Macular Edema After Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; CVD, cardiovascular disease; DME, diabetes mellitus-associated macular edema; ECG, electrocardiogram; ETDRS, Early Treatment of Diabetic Retinopathy Study; EXCITE, Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-Related Macular Degeneration; EXTEND, Safety and Efficacy of Ranibizumab in Japanese Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; FOCUS, Ranibizumab Combined With Verteporfin Photodynamic Therapy in Neovascular Age-Related Macular Degeneration; IVAN, Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization; MANTA, Avastin Versus Lucentis in Age Related Macular Degeneration; MARINA, Minimally Classic/Occlud Trial of the Anti-VEGF

Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; NR, not reported; PIER, Phase IIb, 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; READ, Ranibizumab for Edema of the Macula in Diabetes; RESOLVE, Safety and Efficacy of Ranibizumab in Diabetic Macular Edema With Center Involvement; RESTORE, Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema; RIDE, Ranibizumab for Diabetic Macular Edema; RISE, Ranibizumab for Diabetic Macular Edema; RVO, retinal vein occlusion; SAILOR, Safety Assessment of Intravitreal Lucentis for AMD; VA, visual acuity.

- ^a Information about AE reporting was considered succinct if the authors did not mention that ATEs were specifically assessed.
- ^b Included in the dose-response study.
- ^c Data for 24 months were used for ranibizumab dose comparison.
- ^d Only data for overall and cardiovascular mortality were included to avoid reporting bias.
- ^e Only the triamcinolone group was considered, because patients in the sham group could receive anti-VEGF alternative treatment during the first year.
- ^f Data for 12 months were used for the ranibizumab dose comparison.

of mAb used, or quality of the studies did not significantly influence treatment effect ($P = .98$, $P = .40$, and $P = .38$ for interaction, respectively) (eTable 2 in the Supplement). No significant difference was observed regarding the risk of major cardiovascular events in the 3 trials directly comparing bevacizumab with ranibizumab (OR, 0.94; 95% CI, 0.59-1.52; $P = .81$; $I^2 = 43%$) (eTable 5 in the Supplement). Low-dose ranibizumab was not associated with a lower risk compared with a high dose of the drug (OR, 0.86; 95% CI, 0.62-1.21; $P = .40$; $I^2 = 0%$) (eTable 6 in the Supplement).

Nonocular Hemorrhage Events

Anti-VEGF mAb treatment did not significantly increase the risk of nonocular hemorrhage events when compared to control, with no significant heterogeneity (OR, 1.42; 95% CI, 0.95-2.13; $P = .09$; $I^2 = 0%$) (Figure 4, eTable 2 in the Supplement). No asymmetry was observed in the funnel plot (eFigure 3 in the Supplement). The results obtained with sensitivity analysis did not change when different methods were used to pool the data (eTable 7 in the Supplement). We found no significant impact of follow-up duration in ranibizumab studies

Figure 2. Risk of Bias Summary for Each Included Study

Trial	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Masking of participants and personnel (performance bias)	Masking of outcome assessment (detection bias)
ABC ⁴²	+	+	+	+
ANCHOR ^{33,34}	?	?	+	+
BOLT ⁵²	+	+	-	-
BRAVO ^{17,53}	+	?	+	+
CATT ^{13,44}	+	+	-	-
CRUISE ^{18,54}	+	?	+	+
Elman et al ⁵⁰	+	+	-	-
EXCITE ⁴¹	?	?	?	?
EXTEND-I ⁴⁰	?	?	-	-
FOCUS ^{35,36}	+	+	-	-
IVAN ⁴⁵	+	+	+	+
MANTA ⁴⁶	+	+	+	+
MARINA ²⁷	+	+	+	+
PIER ^{37,38}	+	+	+	+
READ-2 ⁴⁷	?	?	-	-
RESOLVE ⁴⁸	+	+	+	?
RESTORE ⁴⁹	+	+	+	+
RIDE ⁵¹	+	+	+	+
RISE ⁵¹	+	+	+	+
SAILOR ³⁹	?	?	?	?
Subramanian et al ⁴³	?	+	+	+

See the Table footnote for the expanded names of the studies.

($P = .48$) (eTable 4 in the Supplement). The type of disease or study quality did not influence the treatment effect ($P = .16$ and $P = .75$ for interaction, respectively) (eTable 2 in the Supplement). We observed a significantly increased risk of nonocular hemorrhage events in patients with AMD (OR, 1.57; 95% CI, 1.01-2.44; $P = .04$; $I^2 = 0\%$) but not in those with DME (OR, 0.54; 95% CI, 0.17-1.74; $P = .31$; $I^2 = 0\%$) or RVO (OR, 4.50; 95% CI, 0.40-50.07; $P = .22$). A nonsignificant increase of nonocular hemorrhage was observed with bevacizumab in the only trial¹³ comparing bevacizumab with ranibizumab and reported events in patients with AMD (OR, 2.56; 95% CI, 0.78-8.38; $P = .10$) (eTable 5 in the Supplement). Low-dose ranibizumab was not associated with a lower risk compared with high-dose ranibizumab (OR, 0.92; 95% CI, 0.67-1.26; $P = .61$; $I^2 = 0\%$) (eTable 6 in the Supplement).

Secondary End Points

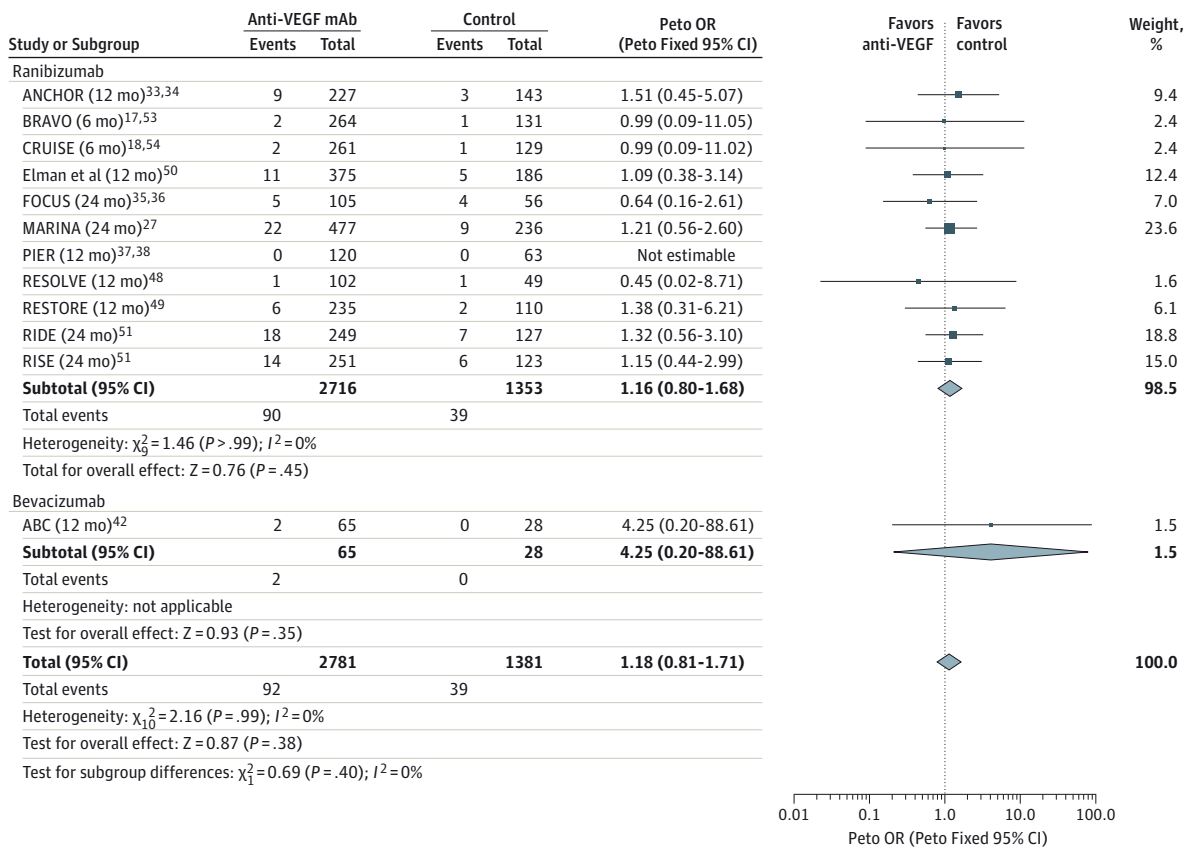
Anti-VEGF treatment did not significantly increase the risks of overall mortality (OR, 1.53; 95% CI, 0.92-2.56; $P = .10$; $I^2 = 0\%$), cardiovascular mortality (OR, 1.29; 95% CI, 0.70-2.37; $P = .42$; $I^2 = 0\%$), stroke (OR, 1.61; 95% CI, 0.85-3.05; $P = .14$; $I^2 = 0\%$), myocardial infarction (OR, 0.92; 95% CI, 0.54-1.59; $P = .77$; $I^2 = 2\%$), hypertension (OR, 0.97; 95% CI, 0.71-1.32; $P = .84$; $I^2 = 6\%$), or VTEs (OR, 1.39; 95% CI, 0.17-11.38; $P = .76$; $I^2 = 0\%$) (eTable 2 in the Supplement). Proteinuria was rarely reported and only in ranibizumab trials. In trials com-

paring bevacizumab vs ranibizumab VTEs were significantly increased with bevacizumab (OR, 3.45; 95% CI, 1.25-9.54; $P = .02$; $I^2 = 0\%$) (eTable 5 in the Supplement). Low-dose ranibizumab was associated with a nonsignificantly lower risk of stroke compared with high-dose ranibizumab (OR, 0.59; 95% CI, 0.34-1.04; $P = .07$; $I^2 = 10\%$) (eTable 6 in the Supplement).

Discussion

To our knowledge, this systematic review and meta-analysis is the first specifically investigating systemic cardiovascular and hemorrhagic adverse events associated with intravitreal administration of anti-VEGF mAbs in a large population of patients included in randomized clinical trials. We considered studies that included patients with AMD, DME, or RVO to increase the power to detect safety signals and because these diseases are the only approved indications for intravitreal anti-VEGF treatment. Although cardiovascular risks may differ among these populations, randomization allows group comparability and relative risk estimation. These conditions are also associated with a high cardiovascular risk (age, diabetes, and associated cardiovascular risk factors). Anti-VEGF treatment adverse vascular events are therefore more likely to be detected in this population at high risk for cardiovascular events.

Figure 3. Forest Plot of Comparisons of Antivascular Endothelial Growth Factor (VEGF) Monoclonal Antibodies (mAbs) With Controls for Major Cardiovascular Events



Diamonds represent pooled estimates of odds ratios (ORs) with horizontal width representing CIs. The size of the data markers indicates the relative

weight of the study. See the Table footnote for the expanded names of the studies.

Our results suggest that intravitreal administration of the anti-VEGF mAbs ranibizumab or bevacizumab was not associated with an increased composite APTC end point compared with control treatments (sham, laser, and other non-anti-VEGF interventions). The effect on each component of the composite end point was not homogenous. We observed non-significant increases in stroke and cardiovascular death risks, but no effect on myocardial infarction. No increased risk of hypertension was apparent, but this end point was heterogeneously reported in clinical trials. The nonsignificant increase in stroke risk observed in our meta-analysis is consistent with previous findings in a pooled analysis of 5 studies in patients with AMD.⁵⁷ Controversial results were published regarding the risk of myocardial infarction and stroke in patients treated with intravitreal anti-VEGF mAbs.⁵⁸⁻⁶² All of these studies were observational (case-control or retrospective cohorts) and therefore subject to biases even if adjustment for confounding factors was performed in some of them.

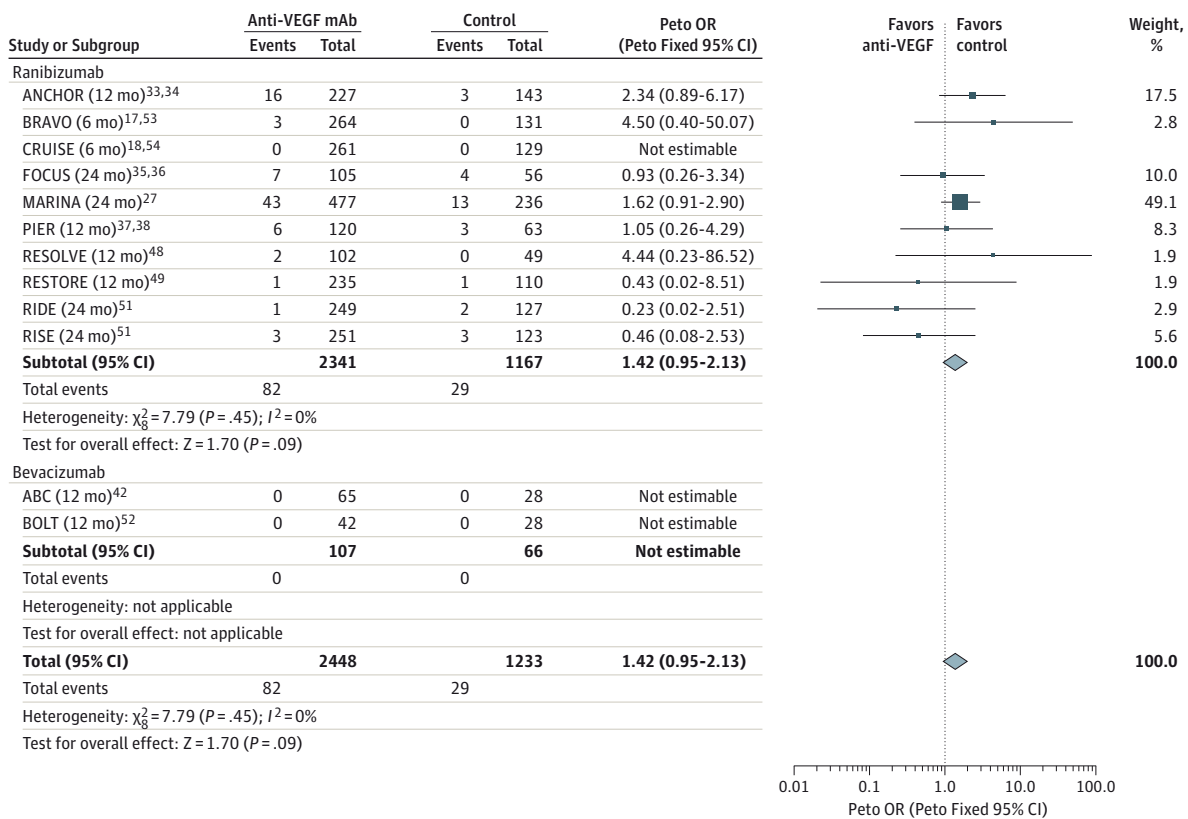
We did not observe any significant differences in APTC risk or in its components between bevacizumab and ranibizumab despite a rationale for a potential risk increase with bevacizumab. Both ranibizumab and bevacizumab undergo systemic passage after intravitreal injection, but only bevacizumab

was associated with a persistent decrease in plasma levels of VEGF in patients with AMD and DME.^{24,63} This is consistent with bevacizumab's pharmacologic profile as a full mAb with a half-life longer than that of ranibizumab. Furthermore, experiments⁶⁴ in animal models suggested that bevacizumab may increase vascular inflammation and platelet activation and therefore the development of thrombosis.

Nonocular hemorrhagic events were not significantly increased with ranibizumab compared with control groups. No hemorrhagic events were reported in bevacizumab vs control studies. The increase in nonocular hemorrhagic risk was significant in patients with AMD who received ranibizumab, consistent with the MARINA²⁷ study results and a recent meta-analysis by Schmucker et al.⁶⁵ This finding could be explained by the confounding effect of age, a factor known to increase bleeding risk in medically ill patients.⁶⁶ No significant hemorrhagic risk was apparent in patients with DME or RVO, but the number of reported events was low.

To our knowledge, this is the first meta-analysis to report VTE risk with intravitreal anti-VEGF treatments compared with control treatments. Only 2 studies^{49,51} reported 4 VTE events with ranibizumab in patients with DME, showing a nonsignificant increase with a very wide CI. When combined, 2

Figure 4. Forest Plot of Comparisons of Antivascular Endothelial Growth Factor (VEGF) Monoclonal Antibodies (mAbs) With Controls for Nonocular Hemorrhage Events



Diamonds represent pooled estimates of odds ratios (ORs) with horizontal width representing CIs. The size of the data markers indicates the relative

weight of the study. See the Table footnote for the expanded names of the studies.

studies^{44,45} showed a significant increase in VTE risk with bevacizumab when directly compared with ranibizumab. An increased VTE risk associated with systemic bevacizumab in patients with cancer has been reported.⁶⁷

A nonsignificant increase in total mortality was apparent with intravitreal anti-VEGF mAbs compared with control treatment, consistent with both ranibizumab and bevacizumab, but this finding should be interpreted with caution, given the limited statistical power of the included studies. A previous meta-analysis²² showed a significant increase in bevacizumab-related mortality in patients with cancer mainly because of hemorrhagic events, but also because of VTE and stroke; however, doses of bevacizumab were much higher and were administered by the systemic route.

Study Limitations

We acknowledge several limitations of our meta-analysis. First, cardiovascular and hemorrhagic events were secondary safety outcomes, and therefore inherently subject to potential detection or reporting bias. These biases were difficult to evaluate because included studies contained limited information on how harms were reported. Four studies only mentioned arteriothrombotic or thromboembolic events as being specifically assessed. Several studies reported zero events, which

could be problematic, but our results were consistent even when using different methods to pool the data. The present review focused on published clinical trial data; publication bias resulting from unpublished trials cannot be excluded even if all tests for funnel plot asymmetry were nonsignificant. We included data from the Elman et al⁵⁰ study, despite reporting of adverse events according to study participants rather than eyes randomized. This resulted in a received-treatment and not intention-to-treat analysis. We believed that the sample size of this study justified its inclusion, even if it could generate potential bias. However, excluding this study did not change our final results (data not shown).

Finally, our results should be interpreted as safety signals that need to be confirmed. Indeed, included studies were of small sample size and therefore not powered enough to show an increase in adverse events risk. Furthermore, the multiplicity of comparisons in this meta-analysis could have led to spurious findings. By using the Framingham risk score we estimated that the baseline risk score of patients with AMD would be approximately 3.5% annually for major cardiovascular events. In this hypothesis, more than 20 000 patients would be necessary to have 80% power to show a 19% increase in APTC risk by anti-VEGF treatment; this population is far more than the 4162 patients included in the APTC evaluation in the

present meta-analysis. The lack of statistical significance of our results may be the result of a lack of effect of these treatments on cardiovascular events, or, as mentioned above, a lack of power of the analysis. Furthermore, the long-term effect of these treatments (>2 years) needs to be evaluated.

Conclusions

Our meta-analysis suggests that intravitreal administration of anti-VEGF mAbs is not associated with significant increases in

risks of systemic cardiovascular and hemorrhagic events or in overall mortality, cardiovascular mortality, or stroke in elderly patients. However, some safety signals, such as nonocular hemorrhagic risk in older patients with AMD observed with ranibizumab and VTE risk with bevacizumab, warrant continued monitoring in sufficiently powered studies. Studies of these safety risks are needed to establish the relative safety of off-label use of bevacizumab compared with ranibizumab and of both drugs compared with placebo.

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