

Risks of Mortality, Myocardial Infarction, Bleeding, and Stroke Associated With Therapies for Age-Related Macular Degeneration

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Objective: To examine associations between therapies for age-related macular degeneration and risks of all-cause mortality, incident myocardial infarction, bleeding, and incident stroke.

Methods: We conducted a retrospective cohort study of 146 942 Medicare beneficiaries 65 years or older with a claim for age-related macular degeneration between January 1, 2005, and December 31, 2006. On the basis of claims for the initial treatment, we assigned beneficiaries to 1 of 4 groups. The active control group included patients who received photodynamic therapy. The other groups included patients who received intravitreal pegaptanib octasodium, bevacizumab, or ranibizumab. We censored data from patients when they received a therapy different from the initial therapy. The main outcome measures were associations between photodynamic, pegaptanib, bevacizumab, and ranibizumab therapies and the risks of all-cause mortality, incident myocardial infarction, bleeding, and incident stroke.

Results: After adjustment for baseline characteristics and comorbid conditions, we found significant differences in the rates of mortality and myocardial infarction by treatment group. Specifically, the hazard of mortality was significantly lower with ranibizumab therapy than with photodynamic therapy (hazard ratio, 0.85; 99% confidence interval, 0.75-0.95) or pegaptanib use (0.84; 0.74-0.95), and the hazard of myocardial infarction was significantly lower with ranibizumab use than with photodynamic therapy (0.73; 0.58-0.92). There were no significant differences in the hazard of mortality or myocardial infarction between bevacizumab use and the other therapies. We found no statistically significant relationship between treatment group and bleeding events or stroke.

Conclusion: Bevacizumab and ranibizumab use was not associated with increased risks of mortality, myocardial infarction, bleeding, or stroke compared with photodynamic therapy or pegaptanib use.

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MORE THAN 1.5 MILLION older Americans have age-related macular degeneration, the most common cause of irreversible vision loss among older patients.¹ Twelve percent have neovascular disease, which accounts for more than 80% of cases of severe vision loss.^{1,2} Before June 2006, the approved pharmacologic therapies for neovascular age-related macular degeneration in the United States were photodynamic therapy with intravenous verteporfin^{3,4} and intravitreal pegaptanib octasodium,⁵ an RNA-based aptamer specific to the vascular endothelial growth factor (VEGF) 165 isoform. Both drugs slow severe vision loss, but few patients experience improved visual acuity. Neither therapy is associated with serious adverse systemic effects.^{5,6}

In June 2006, the US Food and Drug Administration approved ranibizumab for treatment of neovascular age-related macular degeneration.⁷ Moreover, by the fall of 2005, some ophthalmologists were treat-

ing patients with intravitreal injections of bevacizumab, an anti-VEGF agent approved for systemic use in the treatment of some cancers. Initial off-label use of intravitreal bevacizumab was based on a case report describing substantial improvement in visual acuity in a patient with macular edema from central retinal vein occlusion.⁸ Ranibizumab and bevacizumab are derived from the same monoclonal antibody precursor. Bevacizumab is a full-length antibody, whereas ranibizumab is an antibody fragment developed specifically for use in age-related macular degeneration.

Rates of systemic adverse events in randomized controlled trials of ranibizumab were similar to those of placebo or photodynamic therapy.⁸⁻¹¹ In chemotherapy regimens, bevacizumab is associated with an increased risk of thromboembolic events.¹² However, intravitreal bevacizumab is administered at a dose of 1 to 2.5 mg, 150 times less than the systemic dose.¹³ Despite the regulatory approval of ranibizumab, off-label use of bevacizumab con-

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tinues, likely because of the cost difference (\$1950 per dose of ranibizumab vs \$30 per dose of bevacizumab).¹⁴ The relative safety of the therapies is unknown. Therefore, we used a large Medicare claims database to examine associations between therapies for neovascular age-related macular degeneration and risks of all-cause mortality, incident myocardial infarction, bleeding, and incident stroke.

METHODS

DATA SOURCES

We obtained research-identifiable claim files and associated denominator files from the Centers for Medicare and Medicaid Services for all Medicare beneficiaries between January 1, 2004, and December 31, 2007. The inpatient files contain claims data for institutional inpatient services. The outpatient files contain claims data for institutional outpatient services, including emergency department visits that did not result in hospitalization. The physician files contain claims data for physician services and other non-institutional health care encounters. The denominator files contain beneficiary demographic characteristics and information about beneficiary eligibility and enrollment. We limited the study to beneficiaries 65 years or older who were living in the United States, and we limited all analyses to periods of fee-for-service coverage. The institutional review board of the Duke University Health System approved this study.

STUDY POPULATION

We identified beneficiaries who had any claim with a diagnosis of age-related macular degeneration (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 362.16, 362.42, 362.43, or 362.52) between January 1, 2005, and December 31, 2006. For each beneficiary, we then identified the first claim for treatment of age-related macular degeneration.¹⁵ Therapies of interest included photodynamic therapy (*Current Procedural Terminology* [CPT] code 67220) and intravitreal injection (CPT code 67028). The date of first treatment was considered the index date. To gather information about comorbid conditions for risk adjustment, we required 1 year of claims history before the index date. Therefore, the earliest index date was January 1, 2005.

THERAPIES

We classified each patient into 1 of 4 treatment groups based on the claim for the index date. One group was an active control group of patients who underwent photodynamic therapy. The other groups included patients who received pegaptanib, bevacizumab, or ranibizumab. We searched the physician and outpatient claims for each medication. eTable 1 (<http://www.archophthalmol.com>) lists the combinations of service dates, Healthcare Common Procedure Coding System reimbursement codes, and Medicare reimbursement amounts used to identify the medications. Before a medication is assigned a medication-specific reimbursement code, there often is a period during which a generic reimbursement code is used. Because the reimbursement amount differed markedly for each medication, we used the reimbursement amount in combination with the generic reimbursement code to identify medications. We identified all subsequent therapies for age-related macular degeneration in a similar manner. We censored data from patients when they received a therapy different from the one they received initially.

STUDY OUTCOMES

We examined the following 4 adverse events: all-cause mortality, incident myocardial infarction, bleeding, and incident stroke. We measured all-cause mortality using death dates from the denominator files. We identified incident myocardial infarction by searching for inpatient claims or outpatient emergency department claims after the index date that had a primary diagnosis of new myocardial infarction (ICD-9-CM codes 410.x1). We identified bleeding events on the basis of inpatient, outpatient, or physician claims with a diagnosis of hemorrhage anywhere in the claim (ICD-9-CM codes 459.0x, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 569.3x, 578.9x, 623.8x, or 626.8x).^{16,17} Finally, we identified incident stroke by searching for inpatient claims or outpatient emergency department claims after the index date that had a primary diagnosis of stroke (ICD-9-CM codes 430.x, 431.x, 432.x, 434.x, 435.x, or 436.x).¹⁸ We included data for all study outcomes through December 31, 2007. The length of follow-up in all analyses was 1 year after the index date.

OTHER VARIABLES

Medicare beneficiaries report race/ethnicity at the time of enrollment. We used the categories of black or white race/ethnicity and combined other categories and missing values as other/unknown. We identified comorbid conditions by the presence of specific ICD-9-CM codes on any claim in the year before the index date. We searched for diagnoses of cancer, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary heart disease, dementia, diabetes mellitus, hypertension, peptic ulcer disease, peripheral arterial disease, peripheral vascular disease, and renal disease using previously validated coding algorithms.^{19,20}

STATISTICAL ANALYSIS

We describe the characteristics of the treatment groups at the index date by presenting the frequency distributions for categorical variables and the medians and interquartile ranges for continuous variables. We tested for differences between treatment groups using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. We used histograms to summarize the distribution of treatment initiations during the study period.

Estimates of mortality were based on the Kaplan-Meier method. We used the log-rank test to test for mortality differences between the groups. Estimates of myocardial infarction, bleeding, and stroke were based on cumulative incidence estimates,²¹ which account for the competing risk of mortality. We used the Gray test²² to assess differences between the groups on these outcomes. For all 4 outcomes, we censored data from patients when they enrolled in a Medicare managed care plan or when they first received a therapy different from the one they received initially.

For each study outcome, we used Cox proportional hazards regression models to estimate the unadjusted and adjusted effects of all therapies. The unadjusted model included indicators for treatment group only. The adjusted model included indicators for treatment group, demographic characteristics, and comorbid conditions. Given the large number of comparisons, we used a 2-step approach to determine statistical significance. For each outcome, we performed a group test of overall treatment differences. If the group test was significant at $\alpha = .01$, we then examined pairwise comparisons of treatments. We report 99% confidence intervals for all comparisons.

Table 1. Baseline Characteristics of the Study Population by Treatment Group

Variable	Photodynamic Therapy (n = 52 256)	Pegaptanib Octasodium (n = 36 942)	Bevacizumab (n = 38 718)	Ranibizumab (n = 19 026)	P Value ^a
Index year, No. (%)					<.001
2005	40 867 (78.2)	25 719 (69.6)	2 457 (6.3)	0	
2006	11 389 (21.8)	11 223 (30.4)	36 261 (93.7)	19 026 (100.0)	
Age, median (IQR), y	81.0 (76.0-85.0)	81.0 (76.0-85.0)	81.0 (76.0-86.0)	82.0 (77.0-86.0)	<.001
Male sex, No. (%)	18 840 (36.1)	13 100 (35.5)	14 108 (36.4)	6 763 (35.5)	.02
Race/ethnicity, No. (%)					<.001
Black	385 (0.7)	252 (0.7)	422 (1.1)	135 (0.7)	
White	50 879 (97.4)	35 983 (97.4)	37 442 (96.7)	18 547 (97.5)	
Other/unknown	992 (1.9)	707 (1.9)	854 (2.2)	344 (1.8)	
Comorbid conditions, No. (%)					
Cancer	8296 (15.9)	5978 (16.2)	6040 (15.6)	3222 (16.9)	<.001
Cerebrovascular disease	9115 (17.4)	6565 (17.8)	6867 (17.7)	3572 (18.8)	<.001
Chronic obstructive pulmonary disease	13 652 (26.1)	9598 (26.0)	9723 (25.1)	4798 (25.2)	.001
Congestive heart failure	7954 (15.2)	5731 (15.5)	5923 (15.3)	2827 (14.9)	.23
Coronary heart disease	17 857 (34.2)	12 774 (34.6)	12 892 (33.3)	6561 (34.5)	<.001
Dementia	1516 (2.9)	1074 (2.9)	1133 (2.9)	618 (3.2)	.08
Diabetes mellitus	12 843 (24.6)	9260 (25.1)	10 369 (26.8)	4774 (25.1)	<.001
Hypertension	38 661 (74.0)	27 618 (74.8)	28 972 (74.8)	14 483 (76.1)	<.001
Peptic ulcer disease	1125 (2.2)	777 (2.1)	760 (2.0)	391 (2.1)	.25
Peripheral arterial disease	3694 (7.1)	2758 (7.5)	2918 (7.5)	1528 (8.0)	<.001
Peripheral vascular disease	10 170 (19.5)	7305 (19.8)	7838 (20.2)	3942 (20.7)	<.001
Renal disease	2618 (5.0)	2077 (5.6)	2761 (7.1)	1334 (7.0)	<.001

Abbreviation: IQR, interquartile range.

^aP values for continuous variables are by the Kruskal-Wallis test; P values for categorical variables are by the χ^2 test.

By the end of the study period, almost all newly treated patients received bevacizumab or ranibizumab as first-line therapy. Therefore, we performed 2 secondary analyses. First, we limited the study population to new users of bevacizumab or ranibizumab between July and December 2006 and reran the analysis. Second, because of the high coinsurance required of patients who received ranibizumab, there was the possibility of confounding by socioeconomic status. That is, patients with higher socioeconomic status may have been more likely to receive ranibizumab, and, to the extent that these patients were healthier in ways we could not observe, the primary analysis may have been subject to selection bias. To mitigate this potential bias, we reran the analysis after further limiting the study population to patients who received either drug in a medical practice that used a single drug exclusively. We identified these practices by the provider zip code associated with the initial treatment claim. This analysis included practices that performed at least 20 intravitreal injections and for which a single medication represented 95% or more of all intravitreal injections during the third or fourth quarter of 2006.

We used commercially available software (SAS, version 9.2; SAS Institute Inc, Cary, North Carolina) for all statistical analyses.

RESULTS

In 2005 and 2006, a total of 146 942 fee-for-service Medicare beneficiaries underwent first-line treatment for age-related macular degeneration. (Of these, 94 686 received an anti-VEGF agent [eTable 2].⁵) Baseline characteristics of the treatment groups were similar (Table 1). Three-quarters of the patients had hypertension, more than one-third had coronary heart disease, one-fifth had cerebrovascular disease, and one-quarter had diabetes mellitus. Differences in the prevalence of co-

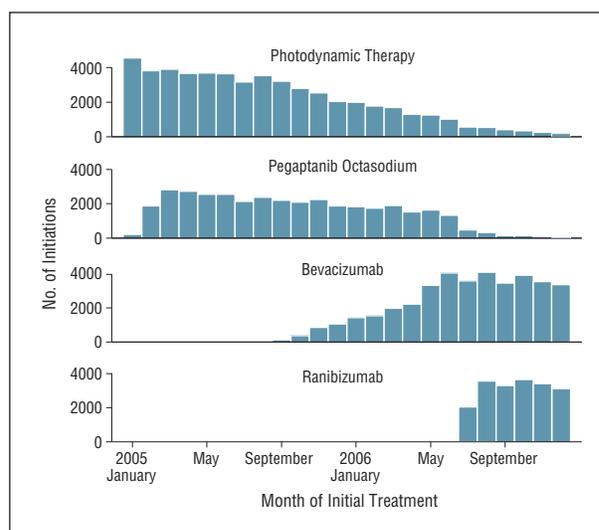


Figure. Number of initiations for each therapy between January 2005 and December 2006.

morbid conditions were statistically significant but not clinically meaningful.

Photodynamic therapy and pegaptanib use as first-line treatment declined during the study period, whereas bevacizumab and ranibizumab use increased substantially. Between July and December 2006, bevacizumab and ranibizumab therapies were used almost exclusively (Figure). Among patients in the photodynamic therapy group, 32.6% (17 023 of 52 256) switched to a different therapy within the year compared with 55.3% patients in the pegaptanib group (20 444 of 36 942), 28.1% in the bevacizumab group (10 887 of 38 718), and 24.0%

Table 2. Cumulative Incidence of Adverse Events at 1 Year by Treatment Group^a

Adverse Event	No. (%)				P Value
	Photodynamic Therapy (n = 52 256)	Pegaptanib Octasodium (n = 36 942)	Bevacizumab (n = 38 718)	Ranibizumab (n = 19 026)	
All-cause mortality	1648 (4.1)	1052 (4.8)	1324 (4.4)	647 (4.1)	.001
Incident myocardial infarction	567 (1.3)	312 (1.3)	378 (1.2)	170 (1.1)	.03
Bleeding	2432 (5.8)	1455 (5.9)	1719 (5.5)	943 (5.8)	.21
Incident stroke	847 (2.0)	482 (2.0)	659 (2.1)	289 (1.8)	.11

^aAll-cause mortality is based on Kaplan-Meier estimates. Incident myocardial infarction, bleeding, and incident stroke are based on estimates of cumulative incidence.

Table 3. Unadjusted and Adjusted Hazards of Adverse Events at 1 Year by Treatment Group

Adverse Event and Treatment 2	Treatment 1 vs Treatment 2, HR (99% CI)			P Value ^a
	Pegaptanib Octasodium	Bevacizumab	Ranibizumab	
Unadjusted Analysis				
All-cause mortality				
Photodynamic therapy	1.16 (1.05-1.28)	1.09 (0.99-1.20)	1.01 (0.90-1.14)	.001
Pegaptanib		0.94 (0.84-1.04)	0.87 (0.77-0.99)	
Bevacizumab			0.93 (0.82-1.05)	
Incident myocardial infarction				
Photodynamic therapy	0.96 (0.80-1.15)	0.90 (0.76-1.07)	0.78 (0.62-0.98)	.03
Pegaptanib		0.94 (0.78-1.15)	0.81 (0.64-1.04)	
Bevacizumab			0.86 (0.68-1.09)	
Bleeding				
Photodynamic therapy	1.03 (0.95-1.13)	0.96 (0.89-1.04)	1.01 (0.92-1.12)	.21
Pegaptanib		0.93 (0.85-1.02)	0.98 (0.88-1.09)	
Bevacizumab			1.05 (0.95-1.17)	
Incident stroke				
Photodynamic therapy	0.99 (0.85-1.14)	1.06 (0.92-1.21)	0.89 (0.75-1.06)	.10
Pegaptanib		1.07 (0.92-1.25)	0.90 (0.74-1.09)	
Bevacizumab			0.84 (0.70-1.01)	
Adjusted Analysis				
All-cause mortality				
Photodynamic therapy	1.01 (0.91-1.12)	0.94 (0.86-1.04)	0.85 (0.75-0.95)	<.001
Pegaptanib		0.93 (0.84-1.04)	0.84 (0.74-0.95)	
Bevacizumab			0.90 (0.79-1.02)	
Incident myocardial infarction				
Photodynamic therapy	0.92 (0.77-1.11)	0.88 (0.74-1.04)	0.73 (0.58-0.92)	.005
Pegaptanib		0.95 (0.78-1.16)	0.80 (0.62-1.02)	
Bevacizumab			0.84 (0.66-1.06)	
Bleeding				
Photodynamic therapy	1.01 (0.92-1.10)	0.94 (0.86-1.02)	0.97 (0.88-1.07)	.14
Pegaptanib		0.93 (0.85-1.02)	0.96 (0.86-1.07)	
Bevacizumab			1.03 (0.93-1.15)	
Incident stroke				
Photodynamic therapy	0.95 (0.82-1.11)	1.02 (0.89-1.17)	0.83 (0.69-0.99)	.02
Pegaptanib		1.07 (0.91-1.25)	0.87 (0.72-1.05)	
Bevacizumab			0.81 (0.68-0.98)	

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aGroup P values are from tests for any treatment effect (with 3 df).

in the ranibizumab group (4558 of 19 026). Overall, among patients who switched therapy, the mean follow-up was 146 days.

There were small differences in the 1-year cumulative incidence of adverse events by treatment group (**Table 2**). There were statistically significant differences in mortality; among beneficiaries who received pegaptanib, 4.8% died compared with 4.4% in the bevacizumab group and 4.1% in the photodynamic therapy and ranibizumab groups. The cumulative incidence of

myocardial infarction was slightly higher in the photodynamic therapy and pegaptanib groups than in the bevacizumab and ranibizumab groups, but the overall P value did not reach statistical significance. There was no statistically significant relationship between treatment group and bleeding events or stroke. Unadjusted hazard ratios for treatment group comparisons of adverse events mirrored the observed differences (**Table 3**).

After adjustment for baseline characteristics and comorbid conditions, we found significant differences in

Table 4. Unadjusted and Adjusted Outcomes at 1 Year for the Comparison of Ranibizumab Therapy vs Bevacizumab Therapy

Adverse Event	No. of Adverse Events/No. (%) of Patients in the Treatment Group		Hazard Ratio (95% Confidence Interval)	
	Ranibizumab	Bevacizumab	Unadjusted	Adjusted ^a
July to December 2006^b				
All-cause mortality	647/19 026 (4.1)	833/21 815 (4.7)	0.87 (0.76-0.99)	0.86 (0.75-0.98)
Incident myocardial infarction	1390/19 026 (1.1)	1793/21 815 (1.3)	0.84 (0.64-1.08)	0.83 (0.64-1.08)
Bleeding	2025/19 026 (5.8)	2403/21 815 (5.6)	1.04 (0.92-1.16)	1.03 (0.92-1.16)
Incident stroke	1471/19 026 (1.8)	1893/21 815 (2.2)	0.80 (0.65-0.97)	0.78 (0.64-0.96)
Exclusive Providers^c				
All-cause mortality	197/4821 (4.7)	225/6147 (4.3)	1.11 (0.87-1.43)	1.10 (0.85-1.41)
Incident myocardial infarction	423/4821 (1.1)	493/6147 (1.3)	0.86 (0.53-1.41)	0.87 (0.53-1.41)
Bleeding	569/4821 (5.3)	651/6147 (5.2)	1.02 (0.81-1.29)	1.01 (0.80-1.28)
Incident stroke	438/4821 (2.1)	529/6147 (2.4)	0.88 (0.62-1.26)	0.87 (0.61-1.24)

^aHazard ratios for ranibizumab compared with bevacizumab after adjustment for the variables listed in Table 1.

^bBy the end of the study period, almost all newly treated patients received ranibizumab or bevacizumab as first-line therapy. Therefore, in this secondary analysis, the study population was limited to newly treated patients who received ranibizumab or bevacizumab between July and December 2006.

^cPatients with higher socioeconomic status may have been more likely to receive ranibizumab vs bevacizumab, so the primary analysis may have been subject to selection bias. Therefore, in this secondary analysis, the study population was limited to patients who received ranibizumab or bevacizumab in a medical practice that performed at least 20 injections and used a single drug in 95% or more of all intravitreal injections during the third or fourth quarter of 2006.

the rates of mortality and myocardial infarction (Table 3). The hazard of mortality was significantly lower with ranibizumab use than with photodynamic therapy or pegaptanib use. The hazard of myocardial infarction was significantly lower with ranibizumab use than with photodynamic therapy. There were no significant differences in the hazard of mortality or myocardial infarction between bevacizumab use and other treatments. For bleeding events or stroke, the overall tests for differences across treatment groups did not reach statistical significance at $\alpha = .01$.

Between July and December 2006, a total of 19 026 patients received ranibizumab and 21 815 received bevacizumab as first-line therapy. Baseline characteristics were similar between the groups, although diabetes mellitus was more common in the bevacizumab group (28.0% vs 25.1%, $P < .001$). **Table 4** gives results of the direct comparisons of ranibizumab therapy vs bevacizumab therapy. The hazards of mortality and stroke were significantly lower with ranibizumab therapy than with bevacizumab therapy.

To mitigate potential selection bias, we further limited the sample to patients newly treated in medical practices that prescribed bevacizumab or ranibizumab exclusively. These groups were similar with respect to baseline characteristics (eTable 3). There were no significant differences in study outcomes between the treatment groups (Table 4).

COMMENT

In early 2006, photodynamic therapy, pegaptanib, and off-label intravitreal bevacizumab were being used for age-related macular degeneration. Neither photodynamic therapy nor pegaptanib use was associated with systemic adverse events.^{5,6} Although systemic bevacizumab for metastatic colorectal cancer was associated with increased risks of thromboembolic events,¹² prospective uncontrolled studies²³⁻²⁶ found no increased risk of adverse systemic effects

after intravitreal injection. More recently, a multinational Internet-based survey of a convenience sample of 70 centers found adverse event rates associated with off-label intravitreal bevacizumab similar to those observed in clinical trial comparison groups.²⁷ In our analysis herein of 146 942 Medicare beneficiaries beginning treatment for age-related macular degeneration between January 2005 and December 2006, we found no increased risk of mortality, myocardial infarction, bleeding, or stroke associated with bevacizumab or ranibizumab use compared with photodynamic therapy or pegaptanib use.

Within 1 month of its approval for treatment of age-related macular degeneration, almost 4000 Medicare beneficiaries received ranibizumab as first-line therapy. As the use of photodynamic therapy and pegaptanib dwindled, the use of bevacizumab continued to increase, likely because of the substantial cost difference between bevacizumab and ranibizumab. Unadjusted comparisons of bevacizumab and ranibizumab suggest a lower risk of mortality and stroke with ranibizumab. After adjustment for patient characteristics, we observed significantly lower hazards of all-cause mortality, incident myocardial infarction, and incident stroke with ranibizumab therapy compared with bevacizumab therapy. Although neither photodynamic therapy nor pegaptanib use was associated with serious adverse systemic effects in randomized controlled trials,^{5,6} the risk of systemic adverse events in our study was lowest with ranibizumab use.

Three possible explanations merit consideration. First, ranibizumab may be protective with respect to mortality and thromboembolic events. Neither animal models nor phase 2 studies support this explanation, and some data suggest that ranibizumab use is associated with an increased risk of stroke.²⁸ Moreover, there is no evidence that photodynamic therapy and pegaptanib use are associated with increased risks of adverse systemic effects. Yet, in our analysis, adjusted risks of mortality and myocardial infarction were significantly lower with ranibizumab use than with photodynamic therapy or pegaptanib use.

Second, because the ranibizumab group did not overlap temporally with the photodynamic therapy and pegaptanib groups, it may be that the risk of thromboembolic events declined in the study population during the study period. This explanation is unlikely. Our analysis covers a short period, and 10% to 15% decreases in the risks of all-cause mortality and incident stroke have not been reported elsewhere to date. Moreover, significant differences in rates of mortality and stroke persisted in the secondary analyses, which we restricted to the limited period during which the availability of ranibizumab and bevacizumab overlapped.

Third, the findings may reflect various selection biases. For example, patients with lower baseline risk for thromboembolic events may have been channeled to ranibizumab therapy over other treatments.²⁹ These data do not support this explanation. Rather, according to the comorbid conditions listed in the claims data, patients who received ranibizumab seem to have been slightly less healthy than patients who received bevacizumab or other therapies. Selective treatment of higher-risk patients with ranibizumab instead of bevacizumab is plausible given concerns about the increased risks of thromboembolic events associated with intravenous bevacizumab.

Alternatively, recipients of ranibizumab may have been healthier in ways we could not measure. The substantial cost difference between ranibizumab and bevacizumab suggests that Medicare beneficiaries with higher socioeconomic status, often associated with better overall health, may have been more likely to receive ranibizumab. A secondary analysis of patients whose physicians prescribed bevacizumab or ranibizumab exclusively provides some evidence for this explanation. Although this analysis addressed the potential treatment selection bias related to socioeconomic status within providers, it did not address potential provider-level confounding by socioeconomic status. Nevertheless, among patients whose physicians used either medication exclusively, the risks of mortality, myocardial infarction, and stroke were not different between the groups. The sample size for this analysis was much smaller than the sample size for the primary analysis, so we cannot know whether the result reflects attenuation of a confounder or loss of statistical power. This explanation regarding the loss of statistical power may be the most likely, but further investigation is warranted.

The event rates that we observed are consistent with previously reported findings.³⁰⁻³² In the most comparable analysis, Alexander and colleagues³² examined annual rates of arterial thromboembolic events among Medicare beneficiaries with new-onset neovascular age-related macular degeneration compared with matched control subjects. Approximately 2.2 per 100 patients with age-related macular degeneration were hospitalized for myocardial infarction during 1 year of follow-up, and 3.9 per 100 patients were hospitalized for hemorrhagic or ischemic stroke. The rates were not significantly different in the control group. In our study, the 1-year cumulative incidence of myocardial infarction ranged from 1.1 to 1.3 cases per 100, and the 1-year cumulative incidence of stroke ranged from 1.8 to 2.1 cases per 100. The higher rates reported by Alexander et al³² may reflect differences between treated and untreated patients. Pre-

sumably, the decision to treat rests on the assumption that the patient will live to experience the benefits.

Our study provides important information about the relative safety of treatments for age-related macular degeneration. Although randomized controlled trials capture data on significant adverse events, they are not powered to detect drug-specific differences in rates of rare adverse events.³³ A National Eye Institute–sponsored comparative trial of the efficacy of ranibizumab and bevacizumab has randomly assigned 1200 patients with newly diagnosed age-related macular degeneration to 1 of 4 treatment groups (2 bevacizumab regimens and 2 ranibizumab regimens).³⁴ Given the baseline risks of thromboembolic events in this population, the sample size that is needed to detect even a 50% relative increase in risk (from 2.0% to 3.0%) would be at least an order of magnitude larger than the trial protocol dictates. As designed, the trial will not adequately assess the relative safety of the 2 therapies.

Our study has some limitations. First, therapies were not randomly assigned; decisions to use a given therapy may have been related to unmeasured confounders. Second, we did not include an untreated control group. We believe that the treated control groups (ie, patients who received photodynamic therapy or pegaptanib) offered fairer comparisons because they excluded patients who were considered ineligible for treatment. Event rates in these groups were similar to those found in untreated control groups. Third, the claims data lacked clinical detail regarding the severity of comorbid conditions and ophthalmologic outcomes. Fourth, a Healthcare Common Procedure Coding System reimbursement code specific to ranibizumab was not assigned until 2008. We applied an algorithm that classified exposure to ranibizumab on the basis of reimbursement codes and payment amounts. Payment amounts for the drugs differed substantially, so misclassification is unlikely.

This study was strengthened by the use of a new-user design¹⁵ and the inclusion of all Medicare fee-for-service beneficiaries newly diagnosed as having age-related macular degeneration and treated in 2005 and 2006.

In conclusion, we found no evidence of increased risks of mortality, myocardial infarction, bleeding, or stroke among Medicare beneficiaries who received intravitreal ranibizumab or bevacizumab for neovascular age-related macular degeneration.

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