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Introducing Anti-Vascular Endothelial Growth Factor Therapies for AMD Did Not Raise Risk of Myocardial Infarction, Stroke, and Death

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Purpose: To assess the effect of availability of anti-vascular endothelial growth factor (VEGF) therapy on mortality and hospitalizations for acute myocardial infarction (AMI) and stroke over a 5-year follow-up period in United States Medicare beneficiaries newly diagnosed with exudative age-related macular degeneration (AMD) in 2006 compared with control groups consisting of beneficiaries (1) newly diagnosed with exudative AMD at a time when anti-VEGF therapy was not possible and (2) newly diagnosed with nonexudative AMD.

Design: Retrospective cohort study.

Participants: Beneficiaries newly diagnosed with exudative and nonexudative AMD in 2000 and 2006 selected from a random longitudinal sample of Medicare 5% claims and enrollment files.

Methods: Beneficiaries with a first diagnosis of exudative AMD in 2006 were the treatment group; beneficiaries newly diagnosed with exudative AMD in 2000 or nonexudative AMD in 2000 or 2006 were control groups. To deal with potential selection bias, we designed an intent-to-treat study, which controlled for nonadherence to prescribed regimens. The treatment group consisted of patients with clinically appropriate characteristics to receive anti-VEGF injections given that the therapy is available, bypassing the need to monitor whether treatment was actually received. Control groups consisted of patients with clinically appropriate characteristics but first diagnosed at a time when the therapy was unavailable (2000) and similar patients but for whom the therapy was not clinically indicated (2000, 2006). We used a Cox proportional hazard model.

Main Outcome Measures: All-cause mortality and hospitalization for AMI and stroke during follow-up.

Results: No statistically significant changes in probabilities of death and hospitalizations for AMI and stroke within a 5-year follow-up period were identified in exudative AMD beneficiaries newly diagnosed in 2006, the beginning of widespread anti-VEGF use, compared with 2000. As an alternative to our main analysis, which excluded beneficiaries from nonexudative AMD group who received anti-VEGF therapies during follow-up, we performed a sensitivity analysis with this group of individuals reincluded (11% of beneficiaries newly diagnosed with nonexudative AMD in 2006). Results were similar.

Conclusions: Introduction of anti-VEGF agents in 2006 for treating exudative AMD has not posed a threat of increased risk of AMI, stroke, or all-cause mortality. *Ophthalmology 2016;123:2225-2231 © 2016 by the American Academy of Ophthalmology.*

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Anti-vascular endothelial growth factor (VEGF) therapies have been shown to be effective in slowing the progression of vision loss among persons diagnosed with exudative age-related macular degeneration (AMD).[1,2] Although the first anti-VEGF agent was approved in 2004, their use became widespread immediately after the introduction of bevacizumab (Genentech, San Francisco, CA) in 2006. Since then, anti-VEGF agents have become first-line therapy for the gamut of retinal vascular diseases. With the growth in use, there has been ongoing concern that anti-VEGF therapies and their extended administration may lead to increased risk of thromboembolic events. Some population-based studies have reported that anti-VEGF treatment of exudative AMD is associated with the development of coronary artery disease and stroke,[3–7] or death associated with long-term use.[8] Furthermore, it has been reported that 30% of persons with exudative AMD without a history of coronary artery disease have a high probability of acute atherothrombotic events.[9] However, other studies have reported no association of anti-VEGF therapies with incident stroke,[10–13] acute myocardial infarction (AMI),[10,13–15] or short-term all-cause mortality.[13,15–18]

Although a recent summary of expert opinion concluded that these agents pose little systemic thromboembolic risk,[19]

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the role of anti-VEGF therapy in mediating thromboembolic events is still insufficiently understood.[20,21] Many prior assessments have lacked adequate power to detect statistically significant differences in these rare adverse outcomes,[22] whereas others were based on the use of local, nonnationally representative samples and short follow-up periods after initiation of anti-VEGF therapy. An additional contributor to such inconclusive results may be the presence of selection bias in individuals treated with anti-VEGF agents. Although treatment with anti-VEGF agents is now common, a combination of issues including patient preferences leading to refusal of treatment, lack of local access, and presence of comorbidities and other conditions make use far from universal. Therefore, observed outcomes may reflect the process of selection into therapy rather than the effect of the therapy on health outcomes.

To deal with the potential problem of selection bias, we designed an intent-to-treat study. Intent-to-treat analysis is intended to control for the effect of nonadherence to prescribed regimens in randomized clinical studies. When applied to longitudinal health records data, in the context of our study, it allows for the treatment of all patients who have the clinically appropriate characteristics to receive anti-VEGF injections, as the treatment group, bypassing the need to monitor whether treatment was actually received.

This study used a nationally representative 5% sample of all US Medicare beneficiaries enrolled in Medicare Parts A and B who were aged 68+ years to assess the effect of the availability of anti-VEGF therapy on all-cause mortality and hospitalizations for stroke and AMI over a 5-year follow-up period in beneficiaries newly diagnosed with exudative AMD compared with beneficiaries newly diagnosed with exudative AMD at a time when anti-VEGF therapy was not possible.

Methods

Data Sources

Data came from a nationally representative 5% random sample of claims filed between January 1, 1997, and December 31, 2013, on behalf of Medicare beneficiaries enrolled in Medicare Parts A and B and residing in the United States. Claims data were linked to an enrollment file providing information on enrollment type and status, dates of birth and death, and basic demographic information. The use of restricted Medicare claims and enrollment data was approved by Duke University's Institutional Review Board and adheres to the ethical principles of World Medical Association Declaration of Helsinki.

Sample Selection

The analysis sample consisted of Medicare beneficiaries first diagnosed with exudative or nonexudative AMD in 2000 and 2006 as recorded on at least 2 Medicare claims within 180 days of each other. Beneficiaries with a first diagnosis of exudative AMD in 2006 were the treatment group, and beneficiaries newly diagnosed with exudative AMD in 2000 or nonexudative AMD in 2000 or 2006 were used as control groups (Table 1). Analysis was restricted to beneficiaries aged 68+ years to allow for a 3-year look-back period, which was used to identify the date of the first exudative or nonexudative AMD diagnosis and to record comorbidities. The date of the first claim with a confirmed study diagnosis was the date used for defining follow-up and look-back periods. The follow-up period was 5 years after the diagnosis date that qualified a beneficiary for inclusion in this study. The study outcomes, death and hospitalizations for stroke and AMI, were evaluated over the follow-up period. Beneficiaries diagnosed with macular edema or retinal vein occlusion over the 5-year follow-up period and beneficiaries with a hospitalization for stroke and/or myocardial infarction over the 3-year look-back period were excluded. In the primary analysis, beneficiaries in the 2006 nonexudative AMD control group who received anti-VEGF therapies during the 5-year follow-up period were excluded (11.1%) (Table 2). A secondary sensitivity analysis with these individuals included also was performed. Most beneficiaries in the 2006 exudative AMD treatment group (53.3%) received anti-VEGF therapy at some time during the 5-year follow-up period after an initial diagnosis of exudative AMD. The 2000 and 2006 cohorts refer to the year of initial diagnosis, not to the year(s) of receipt of anti-VEGF injections, which could occur anytime during the 5-year follow-up period. After excluding beneficiaries

Table 1. List of Study Codes

Condition	Administrative Code*	
Dependent Variables		
Myocardial infarction†	ICD-9:	410.xx 412.xx
Stroke†	ICD-9:	431.xx 434.xx 436.xx
AMD		
Nonexudative senile macular degeneration	ICD-9:	362.51
Exudative senile macular degeneration	ICD-9:	362.52
Exclusions		
Retinal vein occlusion	ICD-9:	362.35 362.36
Macular edema	ICD-9:	362.07 362.53 362.83
Covariates		
Diabetes mellitus, type 2	ICD-9:	250.xx
Hypertension	ICD-9:	401.xx
Atrial fibrillation or flutter	ICD-9:	427.31 427.32
Ischemic heart disease	ICD-9:	411.81 411.89 414.0x 414.8 414.9
Angina	ICD-9:	413.xx
Congestive heart failure	ICD-9:	402.x1 404.x1 428.xx 398.91
Cerebral ischemic attack	ICD-9:	437.1
Transient ischemic attack	ICD-9:	435.x
Intravitreal injection of anti-VEGF agent	CPT-4:	67028 followed by 1 of: J9035 Q2024 C9257 C9399 J3490 J3590 (bevacizumab [Avastin; Genentech, Inc., San Francisco, CA]), C9233 J2778 (ranibizumab [Lucentis; Genentech, Inc.]), J2503 (pegaptanib [Macugen; Valeant Pharmaceuticals, Inc., Laval, Quebec, Canada]), Q2046 C9291 J0178 (aflibercept [Eylea; Regeneron, Inc., Tarrytown, NY]).

CPT-4 = Current Procedural Terminology 4th Edition; ICD-9 = International Classification of Diseases, 9th Revision; VEGF = vascular endothelial growth factor.
*Codes are drawn from ICD-9, Clinical Modification (ICD-9 for condition) and CPT-4 codes.
†Includes Part A inpatient claims only.