

Trends of Anti-Vascular Endothelial Growth Factor Use in Ophthalmology Among Privately Insured and Medicare Advantage Patients

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Purpose: To characterize the first 10 years of intravitreal anti-vascular endothelial growth factor (VEGF) medication use for ophthalmic disease, including bevacizumab, ranibizumab, and aflibercept.

Design: A retrospective cohort study using administrative claims data from January 1, 2006 to December 31, 2015.

Subjects: Total of 124 835 patients 18 years of age or over in the United States.

Methods: OptumLabs Data Warehouse, which includes administrative claims data for over 100 million commercially insured and Medicare Advantage individuals, was used to identify patients receiving intravitreal anti-VEGF injections based on Current Procedural Terminology codes.

Main Outcome Measures: Total and annual numbers of intravitreal anti-VEGF injections, as well as injections per 1000 enrolled patients per general category of ophthalmic disease, overall and for each available medication.

Results: There were 959 945 anti-VEGF injections among 124 835 patients from 2006 to 2015. Among all injections, 64.6% were of bevacizumab, 22.0% ranibizumab, and 13.4% aflibercept; 62.7% were performed to treat age-related macular degeneration (AMD), 16.1% to treat diabetic retinal diseases (including 0.9% of all injections that were for proliferative diabetic retinopathy), 8.3% to treat retinal vein occlusions, and 12.9% for all other uses. Use of bevacizumab and ranibizumab for AMD plateaued as of 2011/2012 and decreased thereafter (in 2006, 58.8 and 35.3 injections/1000 AMD patients, respectively; in 2015, 294.4 and 100.7 injections/1000), whereas use of aflibercept increased (1.1 injections/1000 AMD patients in 2011 to 183.0 injections/1000 in 2015). Bevacizumab use increased each year for diabetic retinal disease (2.4 injections/1000 patients with diabetic retinal disease in 2009 to 13.6 per 1000 in 2015) while that of ranibizumab initially increased significantly and then declined after 2014 (0.1 in 2009 to 4.0 in 2015). Aflibercept use increased each year in patients with diabetic retinal diseases and retinal vein occlusions (both <0.1 per 1000 retinal vein occlusion patients in 2011, 5.6 and 140.2 in 2015).

Conclusions: Intravitreal injections of anti-VEGF medications increased annually from 2006 to 2015. Bevacizumab was the most common medication used, despite its lacking U.S. Food and Drug Administration approval to treat ophthalmic disease, and AMD was the most common condition treated. Ranibizumab use declined after 2014 while both the absolute and relative use of bevacizumab and aflibercept increased. *Ophthalmology* 2017;124:352-358 © 2016 by the American Academy of Ophthalmology

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) drugs have revolutionized the practice of ophthalmology.¹ Although the first anti-VEGF drug, bevacizumab (Avastin; Genentech South San Francisco CA), was approved for use by the U.S. Food and Drug Administration (FDA) in 2004 for the treatment of metastatic carcinoma of the colon or rectum,² ranibizumab (Lucentis; Genentech) was approved soon thereafter in 2006 for the treatment of neovascular age-related macular degeneration (AMD). Ophthalmologists quickly determined that bevacizumab was also efficacious for the treatment of neovascular AMD, and that repackaging of the medication at the appropriate dosage

for ophthalmic treatment would allow physicians to administer many treatments from a single oncologic dose vial at relatively low cost.³ In 2011, another anti-VEGF drug, aflibercept (Eylea; Regeneron, Tarrytown, NY) was approved for use by the FDA.⁴

Ranibizumab and aflibercept are currently FDA approved for the treatment of neovascular AMD, diabetic macular edema (DME), diabetic retinopathy (DR) associated with DME, and macular edema secondary to retinal vein occlusion (RVO). Although bevacizumab remains “off label” for purposes of treating ophthalmic disease, it is estimated that ophthalmologists used the medication to treat 51 different

ocular conditions as of the end of the last decade.⁵ Ranibizumab and aflibercept are also used off label for non-FDA-approved ophthalmic conditions, but to a lesser extent, possibly owing to financial considerations.

Despite the lack of FDA approval for ophthalmic disease, data suggest that bevacizumab has a similar efficacy as ranibizumab for the treatment of neovascular AMD. The 2011 publication of the Comparison of Age-Related Macular Degeneration Treatments Trials reported that patients receiving either bevacizumab or ranibizumab had “equivalent effects on visual acuity” at 1 and 2 years.^{6,7} For treatment of DME, the data are less clear. The recent major trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net) comparing all 3 medications (Protocol T) found that, for patients with worse presenting visual acuities, aflibercept was superior to bevacizumab and ranibizumab at 1 year, but that at 2 years aflibercept was superior to bevacizumab, with ranibizumab statistically similar to both medications.⁸

While debate continues regarding the relative effectiveness of anti-VEGF medications for treatment of ophthalmic disease, an important consideration is the substantial discrepancy in drug prices per standard dose: aflibercept costs \$1950 (2.0 mg/0.05 ml), and ranibizumab costs \$1200 for DR-related indications (0.3 mg/0.05 ml) and \$1950 for AMD and retinal venous occlusive disease (0.5 mg/0.05 ml), whereas repackaged bevacizumab costs only ~\$50 per 1.25-mg dose.^{5,8,9} Given the numerous indications, the varied use, and the large differences in cost, our objective was to examine national patterns of anti-VEGF drug use for ophthalmic conditions, characterizing trends and demographic patterns of bevacizumab, aflibercept, and ranibizumab use from 2006 to 2015 among both privately insured and Medicare Advantage patients.

Methods

Data Source

We conducted a retrospective analysis using the OptumLabs Data Warehouse, a large U.S. database that includes administrative claims data from privately insured and Medicare Advantage enrollees.¹⁰ The database is composed of administrative claims for more than 100 million individuals in all 50 states and of all ages and ethnic and racial groups.¹¹ Administrative claims include medical claims for professional (e.g., physician), facility (e.g., hospital), and pharmacy claims. Pursuant to the Health Insurance Portability and Accountability Act, the use of deidentified data does not require Institutional Review Board approval.

Study Sample

We identified all intravitreal injections with an associated anti-VEGF drug code on the same day between January 1, 2006 and December 31, 2015. To identify the study population, we first selected all claims for intravitreal injections using the Current Procedural Terminology code 67028. Anti-VEGF medications associated with intravitreal injections were identified using medication-specific Healthcare Common Procedure Coding System codes (bevacizumab, C9257, S0116, J9035, and Q2024; ranibizumab, J2778, C9233; aflibercept, J0178, Q2046, C9291).

Because the introduction of Healthcare Common Procedure Coding System codes lag behind FDA approval and because bevacizumab lacks a code specific to ocular use, we also included claims for unclassified/miscellaneous drug codes administered on the same day as an injection (J3490, J3590, and C9399).⁹ We assigned these claims to specific drugs using total paid amounts, since the costs differed significantly across drugs.⁹ Total paid amounts capture the sum of the total amount paid by both the enrollee and health plan for the drug. We imputed the identification of unclassified drugs with amounts of <\$200 as bevacizumab, and those with ≥\$1200 as ranibizumab from July 2006 through 2010 and as aflibercept in 2011 through 2015, using methods that have been used in prior studies.^{9,12} Medications under \$200 that were coded as miscellaneous and were and not coded as another medication (i.e., triamcinolone, which is J3300) were characterized as bevacizumab depending on the time frame. In addition, we excluded all unclassified/miscellaneous records with allowed amounts of \$200 to \$1199, which may have indicated another treatment, such as pegaptanib. We restricted the analysis to enrollees who were 18 years or older and required that enrollees had medical coverage at the time of their injection.

Patient Characteristics

To understand the demographic and clinical characteristics of the patients receiving the injections, we used age, sex, race/ethnicity, and census region information and indicators for ocular conditions—AMD, diabetic retinal diseases, or RVO. Reasons for injections were identified using the primary International Classification of Diseases (ICD) Ninth Revision, Clinical Modification (ICD-9-CM) codes and categorized as being treated for AMD (ICD-9 codes 362.50, 362.51, and 362.52 as well as ICD, Tenth Revision [ICD-10] codes H3532, H3531, and H3530), diabetic retinal diseases (ICD-9 codes 250.50, 362.07, 362.02, 250.51, 250.52, 362.01, and 250.00, as well as ICD-10 codes E11351, E11331, E11341, E11311, E10351, E11359, E10331, E10341, E11329, E10359, E10321, E10311, E11339, E1139, E11349, E11319, E10329, E1039, E13321, E13351, E10339, E13359, E10349, E13341, E13349, and all other codes indicating diabetes with retinopathy), or RVO (ICD-9 codes 362.36 and 362.35, as well as ICD-10 codes H34831, H34832, H34812, H34811, E11321, H34813, H34833, H34819, H34839, H3412, H349); all other ICD-9 and ICD-10 codes were categorized as alternative use.

Statistical Analysis

We examined the rates of anti-VEGF characterized over time in the study population by drug and indication. Patient characteristics (age, sex, race, census region) were described using mean (standard deviation) or count (percentage) as appropriate. We calculated annual rates by using the number of anti-VEGF injections as the numerator and the total number of enrolled patients as the denominator. Furthermore, we assessed rates by indication for administration, using the number of anti-VEGF injections per indication as the numerator and per 1000 patients with the condition as the denominator. To ensure that the denominator has the same restrictions as the numerator, only beneficiaries with a primary condition of the following were included: AMD, diabetic eye disease, or RVO. Rates were expressed as the number of anti-VEGF injections per 1000 patients. This rate has been expressed in similar studies examining anti-VEGF drug use.¹³ The authors defined per-patient use as injections per 1000 beneficiaries who were within a broad diagnosis category (i.e., AMD), not the overall pool of beneficiaries. All analyses were conducted using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

Table 1. Intravitreal Anti-Vascular Endothelial Growth Factor Drug Use, 2006 to 2015

	Bevacizumab (N = 620 207)	Aflibercept (N = 128 578)	Ranibizumab (N = 211 160)	Total (N = 959 945)
Age, years				
Mean (standard deviation)	72.3 (13.0)	76.3 (10.8)	74.0 (11.4)	73.2 (12.5)
Median (interquartile range)	75.0 (64.0, 83.0)	79.0 (70.0, 85.0)	77.0 (66.0, 83.0)	76.0 (65.0, 83.0)
Age category (years)				
18–44	21 968 (3.5%)	1618 (1.3%)	3370 (1.6%)	26 956 (2.8%)
45–64	140 608 (22.7%)	16 615 (12.9%)	41 334 (19.6%)	198 557 (20.7%)
65–74	135 640 (21.9%)	28 358 (22.1%)	47 580 (22.5%)	211 578 (22.0%)
75+	321 991 (51.9%)	81 987 (63.8%)	118 876 (56.3%)	522 854 (54.5%)
Sex				
Female	350 710 (56.5%)	74 943 (58.3%)	122 609 (58.1%)	548 262 (57.1%)
Male	269 497 (43.5%)	53 635 (41.7%)	88 551 (41.9%)	411 683 (42.9%)
Race				
Asian American	11 889 (1.9%)	2799 (2.2%)	3399 (1.6%)	18 087 (1.9%)
African American/black	43 347 (7.0%)	7135 (5.5%)	13 727 (6.5%)	64 209 (6.7%)
Hispanic/Latino	35 317 (5.7%)	5308 (4.1%)	10 009 (4.7%)	50 634 (5.3%)
Unknown/other	85 986 (13.9%)	15 265 (11.9%)	27 799 (13.2%)	129 050 (13.4%)
White	443 668 (71.5%)	98 071 (76.3%)	156 226 (74.0%)	697 965 (72.7%)
Diagnosis group				
Missing	208 (>0.1%)	7 (>0.1%)	23 (>0.1%)	238
AMD	359 267 (57.9%)	99 450 (77.4%)	143 200 (67.8%)	601 917 (62.7%)
Diabetic retinal disease	110 667 (17.8%)	11 486 (8.9%)	31 922 (15.1%)	154 075 (16.1%)
Retinal vein occlusion	56 060 (9.0%)	7176 (5.6%)	16 707 (7.9%)	79 943 (8.3%)
Alternative use	94 005 (15.2%)	10 459 (8.1%)	19 374 (9.2%)	123 772 (12.9%)
Year				
2006	4609	0	1835	6444
2007	10 235	0	5000	15 235
2008	17 601	0	6805	24 406
2009	32 387	0	10 631	43 018
2010	53 355	0	16 683	70 038
2011	76 058	164	23 166	99 388
2012	97 501	10 042	27 253	134 796
2013	104 269	24 914	41 848	171 031
2014	104 839	33 627	41 295	179 761
2015	119 353	59 831	36 644	215 828

AMD = age-related macular degeneration.

*124 835 unique patients (total number of patients represented in this study).

Results

There were 959 945 intravitreal anti-VEGF injections for 124 835 patients between January 1, 2006 and December 31, 2015, and injections increased every year (Table 1, Fig 1). Bevacizumab injections increased from 4609 in 2006 to 119 353 in 2015, aflibercept injections increased from 164 in 2011 to 59 831 in 2015, and ranibizumab increased from 1835 in 2006 to 41 848 in 2013 before falling to 36 644 in 2015. Bevacizumab accounted for 64.6%, ranibizumab for 22.0%, and aflibercept for 13.4%, although it is important to note that aflibercept was not on the market until 2011.

Of the nearly 1 million anti-VEGF injections, 62.7% were performed for the treatment of AMD, 16.1% were for diabetic retinal diseases (including 0.9% for proliferative diabetic retinopathy [PDR]), 8.3% were for RVO, and an additional 12.9% were performed for alternative uses. Use of both bevacizumab and ranibizumab for AMD peaked in 2011/2012 and decreased thereafter (58.8 and 35.3 injections/1000 AMD patients in 2006, peaking at 338.6 and 137.7 injections/1000, and falling to 294.4 and 100.7 injections/1000 in 2015, respectively), whereas use of aflibercept increased every year (in 2011, 1.1 injections/1000 AMD patients; in 2015, 183.0 injections/1000) (Fig 2). For diabetic retinal disease, bevacizumab use increased each year (2.4

injections/1000 DR patients in 2009, 13.6 injections/1000 in 2015), while that of ranibizumab initially increased and then declined after 2014 (0.1 injections/1000 DR patients in 2009, 6.3 injections/1000 in 2014, 4.0 injections/1000 in 2015) (Fig 3). For RVO, bevacizumab and ranibizumab increased significantly and then began to decline after 2012/2013 (69.2 and 1.3 injections/1000 RVO patients in 2008, peaking at 396.0 and 162.1 injections/1000, falling to 374.5 and 112.2 injections/1000 in 2015, respectively) (Fig 4). Aflibercept use increased each year for patients with diabetic retinal diseases and RVO (0.001 and 0.05 injections/1000 in 2011, 5.6 and 140.2 injections/1000 in 2015, respectively) (Figs 3 and 4). The following conditions accounted for the greatest proportion of the 123 772 anti-VEGF injections for alternative uses: retinal edema not otherwise specified (24 647, 19.9%), retinal neovascularization not otherwise specified (18 584, 15.0%) cystoid macular edema (13 416, 10.8%), and vitreous hemorrhage (2718, 2.2%).

Patients 75 years and older received 54.5% of all injections (51.9%, 63.8%, and 56.3% of all bevacizumab, aflibercept, and ranibizumab injections, respectively). Patients aged 65 to 74 received 22.0% of all injections (21.9%, 22.1%, and 22.5%, respectively). Patients aged 45 to 64 received 20.7% of all injections with a relatively smaller proportion of aflibercept injections than the older age groups (22.7%, 12.9%, and 19.6% of all

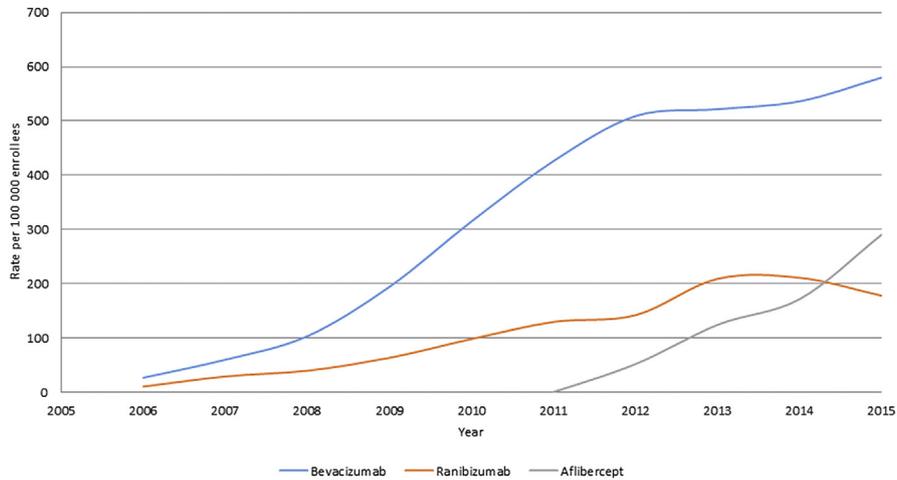


Figure 1. Overall trend in rate of injections per 100 000 enrollees, by drug.

bevacizumab, aflibercept, and ranibizumab injections, respectively). Female patients received 57.1% of injections, while male patients received 42.9%. White patients received 72.7% of injections, patients of unknown or other race 13.4%, African-American/black patients 6.7%, Hispanic/Latino patients 5.3%, and Asian-American patients 1.9%.

Discussion

Over the first 10 years of intravitreal anti-VEGF medication use in the United States, the absolute number of anti-VEGF injections among commercially insured individuals and individuals enrolled in Medicare Advantage, as well as the number of injections per beneficiary, increased every year for bevacizumab, ranibizumab, and aflibercept, until 2014, when overall ranibizumab use began to decline. Bevacizumab accounted for nearly two thirds of all intravitreal anti-VEGF injections. These findings reflect the growing role of anti-VEGF drugs for the treatment of ophthalmic diseases in the United States related to both the

expanding evidence base supporting their efficacy and the expansion of FDA-approved indications. Pharmacologic therapies are now at the forefront of treating retinal diseases, and these data may help inform fiscal considerations as the health care system evolves and alternative reimbursement models are considered.

Our study yielded several observations of interest to the ophthalmic community. First, we observed that the vast majority of anti-VEGF drug use was for AMD, with white elderly patients being more likely to receive anti-VEGF treatment, consistent with the epidemiology of AMD and retinal venous occlusive disease.¹⁴ Second, we found that the rate of ranibizumab use for AMD declined around 2011, a time point that coincides with the release of Comparison of Age Related Macular Degeneration Treatments Trial study 1-year data, as well as FDA approval for aflibercept (Eylea) for the treatment of neovascular AMD.⁶ Third, there have been significant increases in anti-VEGF drug use for diabetic retinal diseases and RVO-associated macular edema, the second- and third-leading indications for anti-VEGF injections.

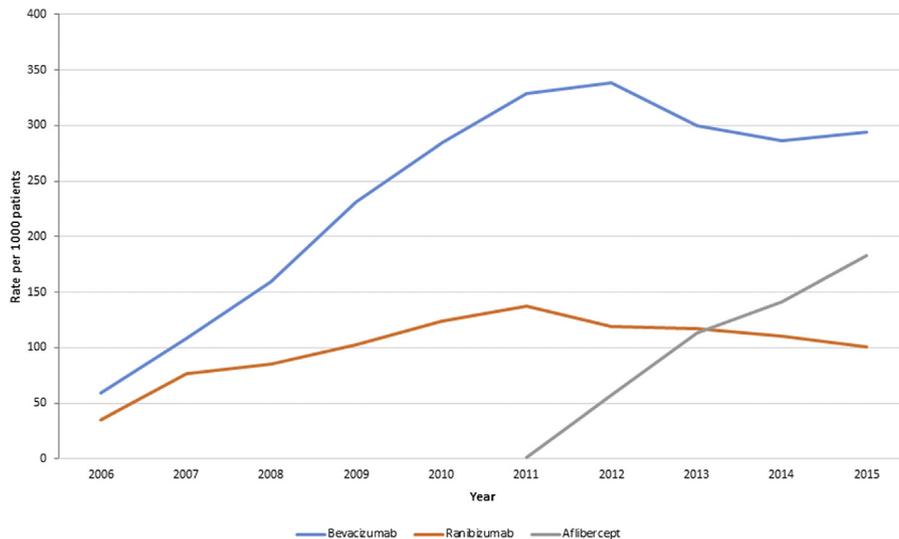


Figure 2. Overall trend in rate of injections by drug per 1000 patients with age-related macular degeneration, 2006 to 2015.

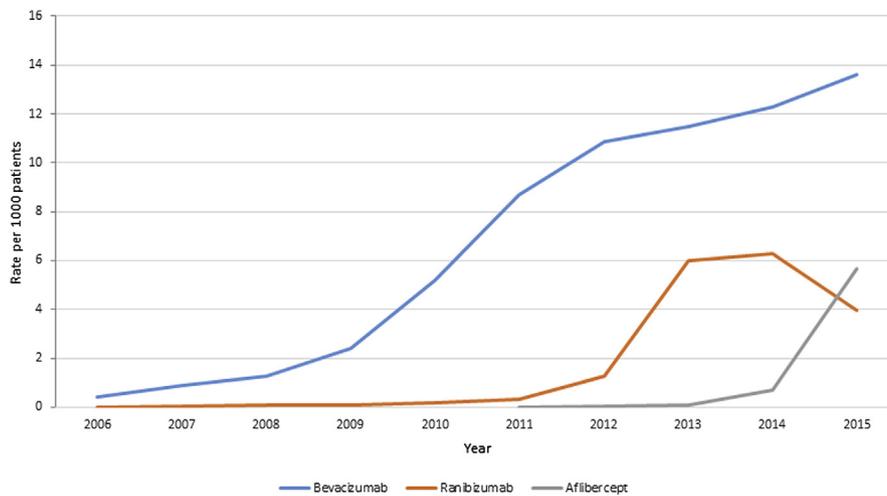


Figure 3. Overall trend in rate of injections by drug per 1000 patients with diabetic retinal disease, 2006 to 2015.

Aflibercept use for these 2 indications increased rapidly in the later years of the study period. The rate of anti-VEGF medication injections for diabetic retinal diseases increased dramatically between 2009 and 2013. The [DRCR.net](#) Protocol I and Ranibizumab for Edema of the mAcula in Diabetes (READ-2) trials first demonstrated superiority of intravitreal anti-VEGF therapy over macular focal/grid laser photocoagulation, with the Protocol I trial also showing superiority of anti-VEGF to intravitreal triamcinolone.^{14,15} The release of these initial reports in 2009 and 2010 coincides with a threefold increase in use of anti-VEGF for diabetic eye disease from 2009 to 2011.^{15,16} Although ranibizumab was the anti-VEGF medication studied in the aforementioned clinical trials, our data show a dramatic increase in bevacizumab use for diabetic retinal diseases over that time frame, as neither ranibizumab nor aflibercept was yet FDA approved or widely reimbursed for those treatment indications.

Ranibizumab use increased exponentially after FDA approval (and widespread payer reimbursement) for the treatment of DME in 2012 at the 0.3-mg dosage following

publication of the Ranibizumab for Diabetic Macular Edema RISE/RIDE trials.¹⁷ The Intravitreal Aflibercept for Diabetic Macular Edema VIVID/VISTA trials led to FDA approval of aflibercept for diabetic macular edema in 2014, with an associated increase in use for diabetic retinal diseases.^{18,19} We also see a large rise in ranibizumab use for RVO-associated macular edema following its FDA approval in 2010 after the Ranibizumab For Macular Edema following Retinal Vein Occlusion BRAVO/CRUISE trials earlier in the year. Aflibercept was subsequently approved by the FDA for treatment of macular edema attributable to central retinal vein occlusion in 2012 and, eventually, branch retinal vein occlusion in 2014.²⁰⁻²² As seen previously in the treatment of AMD, a decline in ranibizumab use occurred following FDA approval of aflibercept for the treatment of both retinal venous occlusive disease and DME.

Indications categorized as alternative use also comprised a sizable proportion, approximately one eighth, of all injections. It is important to note that alternative use is different from off-label use, as “off-label” specifically refers to FDA

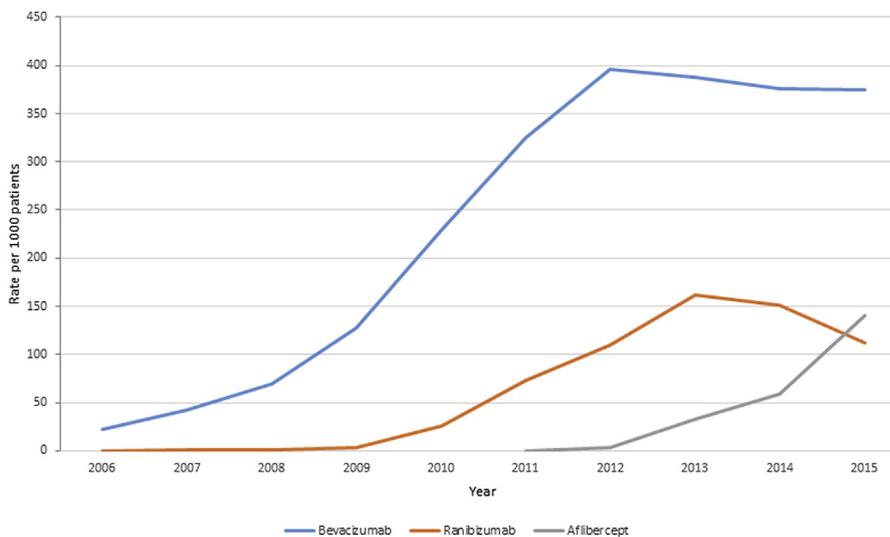


Figure 4. Overall trend in rate of injections by drug per 1000 patients with retinal vein occlusions, 2006 to 2015.

approval at the time of use, and the objective of this study was primarily intended to quantify not on- or off-label use but rather overall trends of anti-VEGF drug use in ophthalmology. Further studies of current alternative uses for anti-VEGF therapy would be beneficial to elucidate whether clinical data support such use, just as trials previously have to expand the use of anti-VEGF beyond only AMD.

The strengths of our study include a large geographically diverse population of over 100 million patients whose age and racial distribution approximates that of the adult U.S. population. In 2015, approximately 19% of the U.S. population in commercial health plans and 19% of those in Medicare Advantage plans were represented in Optum's administrative data assets. Our data set is more diverse and less restrictive than patients enrolled in trials or registries, and includes patients with a broad spectrum of risks who are treated in different settings. However, there are limitations that should be considered as well, including dependence on administrative claims data as well as provider ICD and Current Procedural Terminology coding. In comparing injection rates of anti-VEGF medications for different treatment indications over time, we elected to perform our analyses using the number of injections per 1000 beneficiaries with a given ophthalmic condition (i.e., patients with ICD-9 coding for AMD-related diagnoses). However, the use of diagnostic coding to establish these patient populations has inherent limitations. For this reason, we also performed these comparisons using the overall number of beneficiaries as the denominator, and the resulting trends and relative rates were similar. Another decision was to perform our analyses at the injection level, rather than the patient level, because ophthalmic diseases may involve 1 or both eyes, patients may receive injections of different medications over time in 1 or both eyes, and injections may be performed for different indications in the same or fellow eye. Historically, ophthalmology research has favored the use of eyes as a population denominator, an approach that has been validated and believed to be the most statistically robust.²³

Comparative effectiveness research will likely be an important factor in future trends of anti-VEGF drug use. The DRCR.net Protocol T trial found that, for patients with DME and vision worse than 20/40, aflibercept, a more expensive drug, provides better outcomes than bevacizumab.²⁴ One may speculate that these Protocol T findings will lead to continued increases in aflibercept use. However, relative ranibizumab use may increase, as well, as its 2-year outcomes were similar to those of aflibercept, and at a significantly lower cost for the 0.3-mg ranibizumab DME dose; but it is important to also note that although not well advertised, the visual acuity results between ranibizumab and bevacizumab were also statistically insignificant.²⁴ A similar comparative trial for macular edema following RVO is also underway: the ongoing Study of Comparative Treatments for Retinal Vein Occlusion 2 comparing aflibercept and bevacizumab in patients with RVO. In addition to comparative effectiveness among anti-VEGF drugs, new research comparing anti-VEGF with current non-anti-VEGF gold-standard therapies may also have a profound influence on the trends of anti-VEGF drug use. For example, DRCR.net's Protocol S trial found

ranibizumab to be noninferior to panretinal photocoagulation for PDR, which may lead to an increase in anti-VEGF use for PDR and diabetic retinal diseases as a whole.²⁵

Anti-VEGF drug use is increasing among all groups of patients and for all ophthalmic diseases, not only for FDA-approved uses. Multiple factors may affect anti-VEGF medication choice, including physician and patient financial incentives that favor the use of ranibizumab and aflibercept in certain practice environments and bevacizumab in others. In addition to financial incentives, multiple other factors play a role in medication choice, such as contamination concerns with repackaged and redosed bevacizumab, variation in reimbursement, Medicare patient access to supplemental insurance to cover deductibles, and physician preference. Owing to these multiple and variable influences, a significant geographic variation in both injection rates and relative usage of anti-VEGF medications has developed in the United States.¹⁹ However, our data show that bevacizumab continues to account for the vast majority of anti-VEGF drug use, despite some of the financial incentives that may influence provider use of the more expensive drugs.²⁶ In the most recent year of our study, 2015, bevacizumab use was twice that of aflibercept. However, it is important to note that the rate of aflibercept use is rapidly rising and may likely rise further, especially if aflibercept has superior outcomes in comparative trials. The year 2015 marked the first year that overall aflibercept use exceeded that of ranibizumab in terms of total injections. It will be important to monitor the evolving evidence of comparative effectiveness research, new indications or drugs, and attention to both physician and patient incentives to ensure patients receive both high-quality and cost-effective care in the treatment of retinal diseases.

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Abbreviations and Acronyms:

AMD = age-related macular degeneration; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRCR.net** = Diabetic Retinopathy Clinical Research Network; **FDA** = Food and Drug Administration; **ICD** = International Classification of Diseases; **PDR** = proliferative diabetic retinopathy; **RVO** = retinal vein occlusion; **VEGF** = vascular endothelial growth factor.

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