Original Investigation | CLINICAL SCIENCES

The Effects of Technological Advances on Outcomes for Elderly Persons With Exudative Age-related Macular Degeneration

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IMPORTANCE Exudative age-related macular degeneration (ARMD) is the major cause of blindness among US elderly. Developing effective therapies for this disease has been difficult.

OBJECTIVES To assess the effects of introducing new therapies for treating exudative ARMD on vision of the affected population and other outcomes among Medicare beneficiaries newly diagnosed as having ARMD.

DESIGN The study used data from a 5% sample of Medicare claims and enrollment data with a combination of a regression discontinuity design and propensity score matching to assess the effects on the introduction or receipt of new technologies on study outcomes during a 2-year follow-up period.

SETTING AND PARTICIPANTS The analysis was based on longitudinal data for the United States, January 1, 1994, to December 31, 2011, for Medicare beneficiaries with fee-for-service coverage. The sample was limited to beneficiaries 68 years or older newly diagnosed as having exudative ARMD as indicated by beneficiaries having no claims with this diagnosis in a 3-year look-back period.

EXPOSURES The comparisons with vision outcomes were after vs before the introduction of photodynamic therapy and anti–vascular endothelial growth factor (VEGF) therapy. The comparisons for depression and long-term care facility admission were between beneficiaries newly diagnosed as having exudative ARMD who received photodynamic therapy or anti-VEGF therapy compared with beneficiaries having the diagnosis who received no therapy for this disease.

MAIN OUTCOMES AND MEASURES Onset of decrease in vision, vision loss or blindness, depression, and admission to a long-term care facility.

RESULTS Among beneficiaries newly diagnosed as having exudative ARMD, the introduction of anti-VEGF therapy reduced vision loss by 41% (95% CI, 52%-68%) and onset of severe vision loss and blindness by 46% (95% CI, 47%-63%). Such beneficiaries who received anti-VEGF therapy and were not admitted to a long-term care facility during the look-back period were 19% (95% CI, 72%-91%) less likely on average to be admitted to a long-term care facility during the follow-up period.

CONCLUSIONS AND RELEVANCE This study demonstrates gains in population vision from the introduction of anti-VEGF therapy for patients 68 years or older with an exudative ARMD diagnosis in community-based settings in the United States.

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JAMA Ophthalmol. 2014;132(4):456-463. doi:10.1001/jamaophthalmol.2013.7647
Published online January 23, 2014.

Age-related macular degeneration (ARMD) is a common cause of legal blindness worldwide.[1] The prevalence of exudative ARMD is much lower than that of nonexudative ARMD, but it tends to lead to worse vision outcomes.[2,3] Although common and a major threat to visual health of the elderly, finding effective therapies for exudative ARMD has been a lengthy process. Starting in the 1980s, argon laser photocoagulation therapy (ALPT) was the main treatment option for exudative ARMD.[4-6] In 2000, the US Food and Drug Administration approved photodynamic therapy (PDT) for treating subfoveal choroidal neovascularization.[7] About half a decade later, intravitreal corticosteroids[8,9] became another therapeutic option, but because of their adverse effects profile and questionable effectiveness, they never diffused widely as a treatment for exudative ARMD.[10,11] Vascular endothelial growth factor inhibitors (anti-VEGFs) were first introduced in 2004 with the approval of pegaptanib octasodium by the US Food and Drug Administration.[12,13] However, it was not until the introduction of ranibizumab and bevacizumab in 2006 that the use of anti-VEGF agents gained popularity. Today, anti-VEGF therapy is the treatment of choice for exudative ARMD.[14]

Results of randomized clinical trials indicate that anti-VEGF agents improve the clinical course for many patients,[15,16] at a substantial cost to Medicare. However, only one study to date, based on Danish data,[17]has evaluated the effect of this innovation on visual health at a population level.

The effect of a new technology on population health depends on several factors, including how frequently and competently it is used, the extent to which the technology is applied to patients for whom a change in clinical course can be expected, and what the adherence of patients is to treatment regimens. Even an effective technology will fail to provide a notable effect on population health if it is not applied widely and appropriately.

This study used a regression discontinuity design[18] to assess the effects on vision of introducing 2 technologies for exudative ARMD, namely, PDT and anti-VEGF therapy. The study also analyzed incidence of depression and entry into a long-term care facility following receipt of anti-VEGF therapy.

Methods

Data

The use of restricted Medicare claims data was approved by the Duke University Institutional Review Board. We used data for January 1, 1994, to December 31, 2011, from a randomly selected 5% sample of Medicare beneficiaries. Enrollment information and Medicare claims filed on behalf of beneficiaries were available for the entire sample, allowing for longitudinal tracking. Claims data included information from the following 5 sources: (1) diagnoses (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]), (2) procedures (*Current Procedural Terminology 4* [*CPT-4*]), (3) Health Care Financing Administration Common Procedural Coding System, (4) Centers for Medicare & Medicaid Services provider specialty codes, and (5) dates and place of service codes. Enrollment data included an indicator for enrollment in a Medicare Advantage plan. Also included were data on sex, race/ethnicity, and dates of birth and death (the latter if the beneficiary died during the observation period).

Table 1. List of Condition Codes

Condition	Codes
Exudative ARMD[a]	Source 362.52
Moderate vision loss[a]	Source 369.6x, 369.7x, 369.8x, 369.9x
Severe vision loss[a]	Source 369.1x, 369.2x, 369.3x, 369.4x
Blindness[a]	Source 369.0x
ALPT[a,b]	Source primary diagnosis 362.52 with 67210, 67220, 67228
PDT[a,b]	Source primary diagnosis 362.52 with 67221 (year 2000 only) or 67299 (all years)
Anti-VEGF therapy[b]	Source 67028 with J2503, C9128, J3490, J9035, J3590, C9399, J2778, Q2024
Corticosteroid therapy[b]	Source 67028 with J1870, J1880, J3300, J3301
Diabetes mellitus[a]	Source 250.xx
Diabetic retinopathy[a]	Source 362.01, 362.02
Glaucoma[a]	Source 365.0x-365.5x, 365.60, 365.61, 365 .62, 365.64, 365.65, 365.8x, 365.9x
Cataract[a]	Source 366.xx
Other Eye Diseases	
Diabetic macular edema[a]	Source 362.07
Cystoid macular degeneration/edema[a]	Source 362.53
Histoplasmosis retinitis[a]	Source 115.92
Progressive high myopia[a]	Source 360.21
Retinal neovascularization[a]	Source 362.16
Retinal edema[a]	Source 362.83
Angioid streaks of the choroid[a]	Source 363.43
Rubeosis iridis[a]	Source 364.42
Glaucoma associated with vascular disorders[a]	Source 365.63
Retinal vascular occlusion[a]	Source 362.3x
Chorioretinitis due to toxoplasmosis[a]	Source 130.2x
Depression[a]	Source 296.0x, 296.8x, 296.9x, 300.xx
Admission to a long-term care facility[c]	Source 31, 32, 33

Abbreviations: ALPT, argon laser photocoagulation therapy; ARMD, age-related macular degeneration; CMS, Centers for 2 Medicare and Medicaid Services; *CPT-4*, *Current Procedural Terminology 4*; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

[a] *ICD-9-CM* Code.

[b] *CPT-4* Code.

[c] CMS Service Code.

Sample Selection

We selected beneficiaries with claims indicating a first diagnosis of exudative ARMD (**Table 1**). To allow for a 3-year look-back period and a 2-year follow-up period, we excluded all beneficiaries younger than 68 years at the time of their first diagnosis and those with less than 2 years of data after the date of first diagnosis. We also excluded beneficiaries who were not continuously enrolled during the look-back and follow-up periods because of death, living outside the United States, or en-

rollment in a Medicare Advantage plan. The Medicare Advantage plan enrollees were excluded because Medicare 5% claims are not available on these beneficiaries.

Analysis of the Introduction of PDT and Anti-VEGF Therapy on Vision

For the analysis of visual outcomes, we divided sampled beneficiaries into the following 3 groups: (1) beneficiaries first diagnosed as having exudative ARMD between 1995 and 1998 (the ALPT group), (2) beneficiaries first diagnosed between 2000 and 2003 (the PDT group), and (3) beneficiaries first diagnosed between 2005 and 2008 (the anti-VEGF group). Although early anti-VEGF agents were initially available in 2004, it was not until 2006 that the therapy first gained popularity.[19] Furthermore, pegaptanib, the main anti-VEGF agent used in 2004-2005, was not as effective as the drugs that became available in 2006. Therefore, we considered 2006 the first anti-VEGF treatment year. Because corticosteroids came into use at about the same time that anti-VEGF therapy was first introduced, our analysis could not distinguish between the introduction dates for these 2 innovations, although corticosteroids were much less commonly used than were PDT and anti-VEGF therapy.[14] For this reason, changes in vision at the population level after the introduction of anti-VEGF therapy are attributable to the introduction of this technology rather than to the use of corticosteroids.

Visual outcomes, defined from diagnostic information in claims data for the first 2 years following exudative ARMD diagnosis, were (1) decline in vision and (2) onset of severe vision loss or blindness. Decline in vision was a decrease from normal to moderate, moderate to severe, or severe to blindness. Moderate vision loss was identified by *ICD-9-CM* codes for profound impairment in one eye, moderate or severe impairment in one eye, unqualified visual loss in one eye, and unspecified visual loss (Table 1). Severe vision loss was identified from codes for moderate or severe impairment in the better eye with profound impairment in the worse eye, moderate or severe impairment in both eyes, unqualified visual loss in both eyes, and legal blindness as defined in the United States. Blindness was defined as profound impairment in both eyes.

To assure that patient mix on observed factors was comparable for the periods before and after the new therapy was introduced, we used propensity score matching (PSM)[20] based on the following covariates: age, sex, black race, Hispanic ethnicity, Charlson Comorbidity Index,[21] and diagnosis of diabetes mellitus, diabetic retinopathy, glaucoma (without vascular disorders), cataract, and other eye diseases. All conditions were identified from claims filed in a 3-year look-back period before the date of first exudative ARMD diagnosis.

Beneficiaries who could not be matched using PSM were dropped, yielding final matched samples of 34 386 for the PDT vision decrease analysis and 31 746 for the PDT severe vision loss and blindness analysis; for the anti-VEGF analysis, the sample sizes were 38 769 and 35 726, respectively. Treatment and control groups were considered well matched if the standardized difference was less than 10%.[22-25]

The regression discontinuity method is designed to overcome the statistical problem of endogeneity of an explanatory variable in observational data, in this context a therapeutic intervention. Endogeneity mainly arises in this setting because insufficient information exists about clinical attributes in the claims data that are observable to the provider but not reported by the provider on claims. As a consequence, persons receiving the technology may seem to have worse outcomes. With the regression discontinuity method, the focus is on all persons having the diagnosis rather than the subset of patients receiving the particular treatment for that diagnosis. Therefore, the problem of unobserved clinical attributes of patients selected for treatment does not arise.

For each treatment group–control group sample, we regressed outcome measures on a binary variable for the treatment and the same covariates used for matching. The parameter estimate on the binary explanatory variable for treatment indicated the effect of the introduction of a new technology on a vision outcome. This parameter estimate corresponds to the average treatment effect on the treated in PSM.

Analysis of New Technologies for Exudative ARMD Treatment on Depression and Admission to a Long-term Care Facility

Incident depression was based on whether a primary diagnosis of depression was documented during a 2-year follow-up period among beneficiaries with no diagnosis of depression on a claim during the 3-year look-back period. The dependent variable for incident long-term care facility use was based on US Centers for Medicare & Medicaid Services place of service codes for a skilled nursing facility (code 31), a nursing facility (code 32), and a custodial care facility (code 33) recorded on a claim during the follow-up period, again conditional on the beneficiary having no such claim during the look-back period.

Many other factors contribute to population-level effects on depression and long-term care facility use than just the introduction of a new therapeutic technology, which made a regression discontinuity design unsuitable for these outcomes. Because unobserved attributes of the eye are less likely to be determinants of depression and long-term care facility use, endogeneity was not as major a concern. Hence, beneficiaries in the depression and long-term care facility analysis samples were defined as treated if they had received a particular therapy within 1 year of first exudative ARMD diagnosis and as control subjects if they had received no therapy. We excluded from the treatment group beneficiaries who had received more than 1 type of therapy for ARMD during the 2-year follow-up period. Beneficiaries receiving ALPT or corticosteroid therapy were excluded from the treatment and control groups.

Sample sizes for the analysis of onset of depression and entry into a long-term care facility were substantially smaller than those for visual outcomes because the former was limited to the subset of sampled beneficiaries actually receiving PDT or anti-VEGF therapy. No statistically significant results were observed for receipt of PDT in the depression or admission to long-term care facility analyses. Hence, the results are not shown below.

Table 2. Decline in Vision: Sample Characteristics Before and After Propensity Score Matching

Covariate[a]	Before Matching			After Matching		
	PDT Group (n = 34 386)	ALPT Control Group (n = 34 386)	Standardized Difference	PDT Group (n = 31 746)	ALPT Control Group (n = 31 746)	Standardized Difference
PDT						
Age, years	80.01	79.58	6.62	79.70	79.60	1.62
Male sex	0.34	0.34	0.04	0.34	0.34	−0.55
Black race	0.02	0.02	−3.74	0.02	0.02	−0.71
Hispanic ethnicity	0.01	0.01	2.00	0.01	0.01	−0.46
Charlson Index	2.22	2.04	8.68	2.02	2.04	−0.98
Diabetes mellitus	0.25	0.21	11.05	0.20	0.21	−0.33
Diabetic retinopathy	0.06	0.04	4.80	0.04	0.05	−0.92
Glaucoma	0.24	0.22	4.73	0.22	0.22	−0.17
Cataract	0.69	0.69	0.56	0.70	0.69	1.48
Other eye disease	0.21	0.20	4.42	0.19	0.20	−0.91
	PDT Group (n = 38 769)	ALPT Control Group (n = 38 769)	Standardized Difference	PDT Group (n = 35 726)	ALPT Control Group (n = 35 726)	Standardized Difference
Admission to a Long-term Care Facility						
Age, years	80.86	80.08	11.78	80.38	80.28	1.54
Male sex	0.33	0.34	−2.39	0.34	0.34	0.21
Black race	0.02	0.02	0.49	0.02	0.02	0.34
Hispanic ethnicity	0.01	0.01	4.77	0.01	0.01	−1.25
Charlson Index	2.14	2.26	−5.78	2.18	2.20	−0.96
Diabetes mellitus	0.32	0.26	12.42	0.28	0.27	2.23
Diabetic retinopathy	0.07	0.06	4.32	0.06	0.06	−0.65
Glaucoma	0.27	0.24	7.90	0.26	0.24	2.83
Cataract	0.63	0.68	−10.35	0.67	0.67	−0.52
Other eye disease	0.20	0.21	−1.13	0.20	0.20	−0.60

Abbreviations: ALPT, argon laser photocoagulation therapy; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

[a] Age and Charlson are means of continuous variables. The remaining variables are mean values of binary variables, ie, fractions.

Results

Analysis of Vision Decrease and Onset of Severe Vision Loss or Blindness

Even before PSM, the PDT and ALPT groups and the anti-VEGF and PDT groups used in the analysis of vision decrease were similar at first exudative ARMD diagnosis, with a few exceptions (**Table 2**). The exceptions were the proportions of the sample having a diabetes mellitus diagnosis (top of the table) and age and the proportions having diabetes mellitus and cataract diagnoses (bottom of the table). Sample proportions with diabetes mellitus are higher at the bottom than at the top, reflecting a positive secular trend in diabetes prevalence. The mean age was approximately 80 years, roughly two-thirds of the sample were female, about 2% were black, and on average 1% were Hispanic. After matching, all standardized differences were well under the 10% threshold for a satisfactory match in PSM. Sample characteristics for the analysis of onset of severe vision loss or blindness were similar to those of the decline in vision analysis sample and are not shown.

In the PDT sample, 3.0% of beneficiaries experienced decreased vision as documented in the claims data in the 2 years following a first exudative ARMD diagnosis (**Table 3**). The corresponding percentage in the anti-VEGF sample was 2.7%. Judging from the odds ratio (OR) on the covariate for treatment, the odds of decreased vision increased by 21% following the introduction of PDT (OR, 1.21; 95% CI, 1.06-1.38). By contrast, the odds of decreased vision fell by 41% following the introduction of anti-VEGF therapy (OR, 0.59; 95% CI, 0.52-0.68).

Vision loss or blindness was first diagnosed in 2.1% of beneficiaries in the PDT sample and in 2.0% of beneficiaries in the anti-VEGF sample in the 2 years following a first exudative ARMD diagnosis. The result for PDT again implies that the introduction of PDT increased the probability of vision loss (OR, 1.40; 95% CI, 1.19-1.63), while the introduction of anti-VEGF therapy showed a strong protective effect, a 46% reduction (OR, 0.54; 95% CI, 0.47-0.63).

Analysis of Depression and Admission to a Long-term Care Facility

The depression analysis sample contained no standardized differences greater than 10% even before matching (**Table 4**). In the long-term care facility admission analysis sample, the only standardized difference before matching was for age. After matching, all standardized differences were below the 10% threshold.

Table 3. Vision Change Before and After the Introduction of PDT and Anti-VEGF Therapy

Covariate	Odds Ratio (95% CI)			
	Decline in Vision		Onset of Severe Vision Loss or Blindness	
	PDT Group (n = 31 746)	Anti-VEGF Therapy Group (n = 35 726)	PDT Group (n = 31 536)	Anti-VEGF Therapy Group (n = 35 400)
Treatment	1.21 (1.06-1.38)[a]	0.59 (0.52-0.68)[a]	1.40 (1.19-1.63)[a]	0.54 (0.47-0.63)[a]
Age	1.01 (0.99-1.02)	1.02 (1.01-1.03)[a]	1.02 (1.01-1.03)[a]	1.03 (1.01-1.04)[a]
Male sex	0.83 (0.72-0.96)[b]	0.90 (0.79-1.04)	0.91 (0.77-1.08)	0.90 (0.77-1.06)
Black race	0.49 (0.25-0.96)[b]	0.70 (0.39-1.25)	0.47 (0.21-1.05)	0.62 (0.31-1.26)
Hispanic ethnicity	0.63 (0.23-1.69)	1.26 (0.67-2.39)	0.68 (0.22-2.14)	1.62 (0.83-3.18)
Charlson Index	1.02 (0.99-1.05)	1.03 (1.00-1.06)	0.99 (0.96-1.04)	1.02 (0.98-1.05)
Diabetes mellitus	1.02 (0.85-1.22)	0.87 (0.74-1.03)	0.90 (0.72-1.13)	0.83 (0.68-1.01)
Glaucoma	1.13 (0.97-1.31)	1.01 (0.87-1.17)	1.28 (1.07-1.53)[a]	1.12 (0.94-1.32)
Diabetic retinopathy	0.84 (0.59-1.20)	1.09 (0.81-1.47)	1.24 (0.84-1.83)	1.24 (0.89-1.74)
Cataract	1.18 (1.02-1.37)[b]	0.87 (0.76-0.99)[b]	1.10 (0.93-1.31)	0.87 (0.75-1.02)
Other eye disease	1.46 (1.25-1.69)[a]	1.27 (1.09-1.48)[a]	1.42 (1.19-1.70)[a]	1.21 (1.01-1.45)[a]

Abbreviations: PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

[a] $P < .01$.

[b] $P < .05$.

Table 4. Depression and Long-Term Care Facility Admissions With and Without Anti-VEGF Therapy: Sample Characteristics Before and After Propensity Score Matching

Covariate[a]	Before Matching			After Matching		
	Anti-VEGF Therapy Group (n = 15 561)	No Treatment Control Group (n = 15 561)	Standardized Difference	Anti-VEGF Therapy Group (n = 13 258)	No Treatment Control Group (n = 13 258)	Standardized Difference
Depression						
Age, years	81.09	80.60	7.27	81.10	81.12	−0.36
Male sex	0.35	0.35	1.19	0.35	0.34	2.57
Black race	0.01	0.02	−6.67	0.01	0.01	2.18
Charlson Index	2.02	2.13	−5.45	2.02	1.92	4.88
Diabetes mellitus	0.31	0.33	−4.99	0.31	0.29	4.75
Diabetic retinopathy	0.06	0.07	−4.00	0.06	0.05	4.45
Glaucoma	0.25	0.29	−7.26	0.25	0.25	1.67
Cataract	0.64	0.62	3.08	0.64	0.64	0.28
Other eye disease	0.22	0.18	9.78	0.22	0.20	5.47
	Anti-VEGF Therapy Group (n = 14 300)	No Treatment Control Group (n = 14 300)	Standardized Difference	Anti-VEGF Therapy Group (n = 12 282)	No Treatment Control Group (n = 12 282)	Standardized Difference
Admission to a Long-term Care Facility						
Age, years	80.53	79.85	10.43	80.55	80.58	−0.54
Male sex	0.36	0.35	0.83	0.36	0.35	1.77
Black race	0.01	0.02	−7.47	0.01	0.01	1.01
Charlson Index	1.92	1.98	−3.11	1.92	1.82	5.05
Diabetes mellitus	0.30	0.31	−3.40	0.30	0.27	5.88
Diabetic retinopathy	0.06	0.07	−4.43	0.06	0.04	6.32
Glaucoma	0.25	0.29	−8.03	0.25	0.25	−0.22
Cataract	0.65	0.64	2.92	0.65	0.66	−1.13
Other eye disease	0.22	0.19	9.42	0.22	0.21	4.56

Abbreviation: VEGF, vascular endothelial growth factor.

[a] Age and Charlson are means of continuous variables. The remaining variables are mean values of binary variables, ie, fractions.

A first diagnosis of depression during the follow-up period occurred in 2.0% of the eligible study population (**Table 5**). No statistical difference was observed in the probability of a first depression diagnosis among beneficiaries with an exudative ARMD diagnosis who received anti-VEGF therapy and those who did not. Men were 42% less likely to be diagnosed as having depression for the first time during the follow-up period (OR, 0.58; 95% CI, 0.44-0.78); each additional point on the

Charlson Comorbidity Index (mean value, approximately 2) led to an increase of 6% in the probability of a first depression diagnosis (OR, 1.06; 95% CI, 1.00-1.13).

One-tenth (10.1%) of beneficiaries with a first exudative ARMD diagnosis were admitted to a long-term care facility during the follow-up period, conditional on not having been admitted to such facilities during the look-back period. Receipt of anti-VEGF therapy was associated with a 19% lower probability of entry into a long-term care facility (OR, 0.81; 95% CI, 0.72-0.91). Older age (OR, 1.10; 95% CI, 1.09-1.11) and higher values on the Charlson Comorbidity Index (OR, 1.10; 95% CI, 1.07-1.13) increased the probability of admission, while male sex (OR, 0.68; 95% CI, 0.60-0.78) decreased it. Therefore, anti-VEGF treatment had about the same effect on the probability of being admitted to a long-term care facility as did doubling of the Charlson Comorbidity Index from its observational mean.

Table 5. Outcomes of Depression and Admission to a Long-term Care Facility

Covariate	Odds Ratio (95% CI)	
	Depression (n = 13 258)	Admission to a Long-term Care Facility (n = 12 282)
Treatment	0.90 (0.71-1.15)	0.81 (0.72-0.91)[a]
Age	1.02 (0.99-1.04)	1.10 (1.09-1.11)[a]
Male sex	0.58 (0.44-0.78)[a]	0.68 (0.60-0.78)[a]
Black race	0.58 (0.14-2.38)	1.02 (0.60-1.75)
Charlson Index	1.06 (1.00-1.13)[b]	1.10 (1.07-1.13)[a]
Diabetes mellitus	1.11 (0.82-1.49)	1.02 (0.88-1.19)
Glaucoma	0.88 (0.66-1.17)	1.06 (0.93-1.22)
Diabetic retinopathy	1.04 (0.61-1.78)	1.26 (0.95-1.68)
Cataract	1.08 (0.83-1.40)	0.88 (0.78-1.00)
Other eye disease	1.08 (0.80-1.46)	0.98 (0.84-1.15)

[a] $P < .01$.

[b] $P < .05$.

Discussion

Our study yielded 2 key findings. First, the introduction of anti-VEGF therapy reduced vision loss and onset of severe vision loss and blindness in a national longitudinal sample of US elderly newly diagnosed as having exudative ARMD. Second, such beneficiaries who received anti-VEGF therapy and were not admitted to a long-term care facility during the 3-year look-back period were substantially less likely to be admitted to a long-term care facility during a 2-year follow-up period. To our knowledge, this is the third study (after Bloch et al[17] and Skaat et al[16]) to demonstrate gains in population visual health for patients having an ARMD diagnosis and is the first study to demonstrate this for the United States or other large high-income countries and document gains in vision specifically for exudative ARMD. Furthermore, our study benefited from being based on a large national longitudinal sample of US elderly and using statistical techniques (including PSM and a regression discontinuity design) and controlling for common confounders designed to mitigate endogeneity of treatment.

The only other studies documenting trends in visual outcomes at a population level are comparisons of legal blindness in Denmark[17] and Israel.[16] Rates of legal blindness among persons in Denmark 50 years and older having an ARMD diagnosis (not just exudative ARMD) fell by 50% between 2000 and 2010, with most of the decline occurring after 2006 (ie, soon after anti-VEGF therapy was introduced).[17] Our results for severe vision loss or blindness, a broader definition of vision loss, imply approximately half as much improvement as in the Danish study. We used a narrower age range, and our results applied only to new diagnoses of exudative ARMD with outcomes observed during a 2-year follow-up period. Although smaller than the Danish study, the present study nevertheless indicates substantial improvements in vision for the population of US elderly newly diagnosed as having exudative ARMD following the introduction of anti-VEGF therapy. A study[16] conducted in Israel also showed a decline in age-standardized rates of certification of blindness among persons with an ARMD diagnosis starting in 2004. The rate of decline was somewhat larger from 2004 to 2006 than from 2006 to 2008. Although no data on volume of anti-VEGF procedures were presented, as in the United States, volume increases from 2006 to 2008 presumably substantially exceeded those from 2004 to 2006. Therefore, the higher rate of decline from 2004 to 2006 than from 2006 to 2008 in Israel is puzzling.

Rather than relying on a single database, as in this study, Bressler and colleagues[26] applied evidence on visual acuity outcomes from phase 3 ranibizumab clinical trials to incidence rates of exudative ARMD from population-based data sources. The effect sizes were larger than those in our study, possibly because visual outcomes are better measured in trials than in claims data. However, it is also possible that true underlying effect sizes in a controlled environment of a trial exceed the effect sizes in community settings.

Previous studies[27-29] have documented a link between depression and ARMD. Our study related receipt of anti-VEGF therapy to incident diagnosis of depression. Receipt of anti-VEGF therapy did not lead to statistically significant reductions in newly diagnosed depression during the follow-up period. A relationship is also documented between ARMD and vision loss more generally and long-term care facility use.[29-31] In this study, we report a reduction in long-term care facility admissions in the 2 years following first receipt of anti-VEGF therapy.

The use of Medicare claims data in health outcomes research has several well-known limitations.[32,33] In particular, claims data are used for the purpose of paying providers of care, and diagnostic information must be provided only to the extent that it supports a claim for payment of care rendered. Although procedure coding is presumably accurate as a matter of law, diagnostic information is limited by available codes and may be provided only in detail sufficient for obtaining payment. Diagnostic codes descriptive of visual acuity are not needed for payment, and this raises the question as to their accuracy and most directly the possibility of undercoding of

visual acuity and the diagnosis of blindness.[32-34] One study[34] assessed the quality of such data in Medicare claims, concluding that the prevalence estimates derived from such data are consistent with data provided by epidemiologic studies.

Another issue is the absence of eye-specific codes in the *ICD-9-CM* system. Therefore, we lacked the ability to measure the spread of exudative ARMD to the second eye using Medicare claims data. It has been estimated that on average patients with exudative ARMD in one eye will experience involvement of the second eye at a rate of approximately 10% per year.[35] Therefore, this underascertainment is exacerbated by the short 2-year follow-up period used in this study. Even so, this limitation implies that our estimates are likely to be, if anything, downward biased.

Conclusions

In sum, the introduction of anti-VEGF therapy has led to important improvements in visual health among elderly persons newly diagnosed as having exudative ARMD and to reductions in long-term care facility use. Such effects are not just observable in randomized controlled trials but, as this study shows, are seen in the population of individuals having this disease. The reductions in long-term care facility use attributable to the use of anti-VEGF therapy are important not only because of their implications for health care spending but also for the improvement in functional status that underlies the reductions and is not measured well by *ICD-9-CM* or *CPT-4* codes.

ARTICLE INFORMATION

Submitted for Publication: April 25, 2013; final revision received October 7, 2013; accepted October 22, 2013.

Published Online: January 23, 2014. doi:10.1001/jamaophthalmol.2013.7647.

Author Contributions: Dr Sloan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition of data: Sloan.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Sloan.
Statistical analysis: All authors.
Obtained funding: Sloan.
Administrative, technical, or material support: Sloan.
Study supervision: Sloan.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported in part by grant R01-AG017473 from the National Institute on Aging (Dr Sloan and Mr Hanrahan).

Role of the Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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